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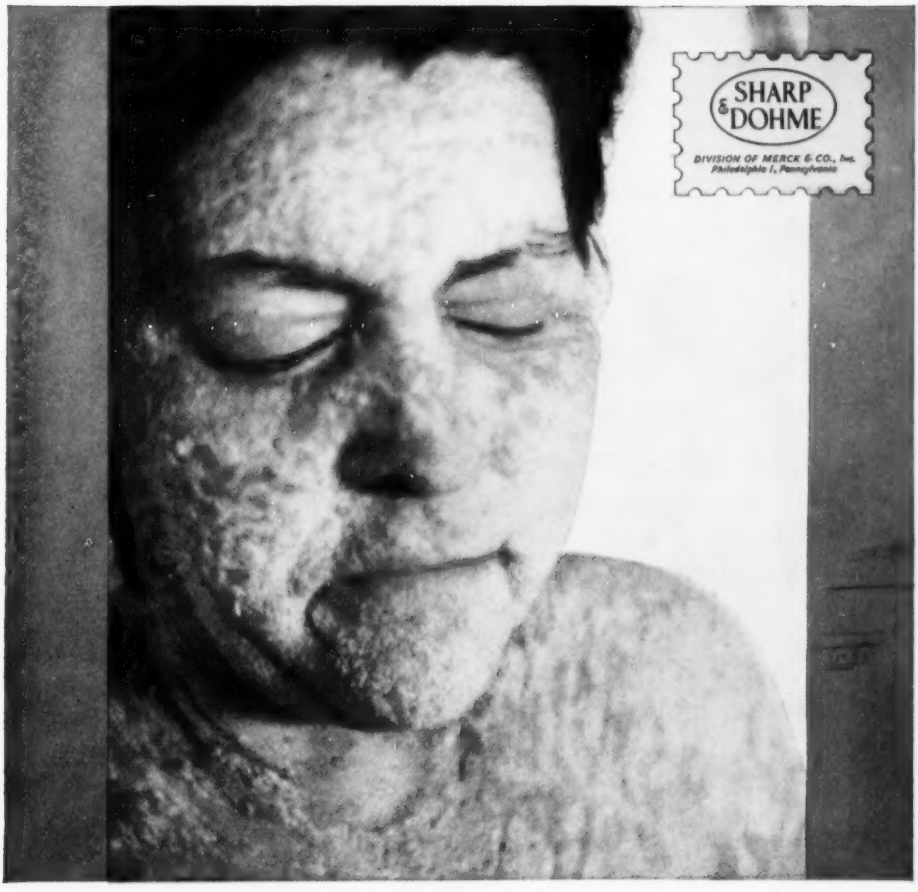

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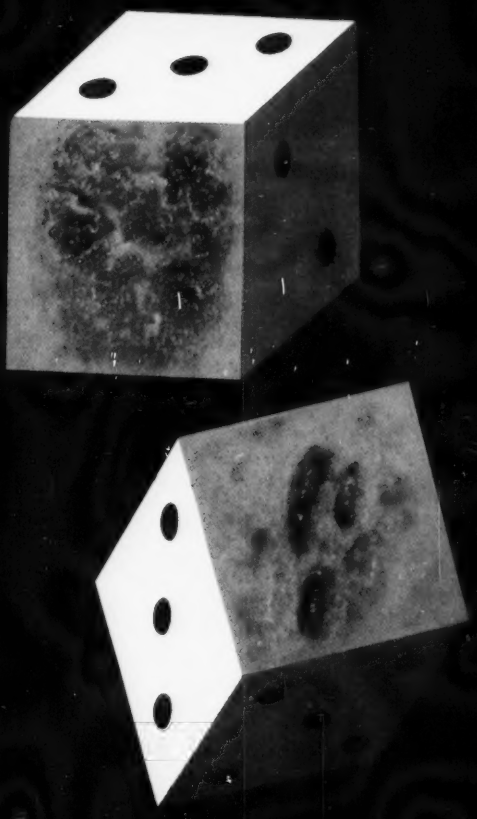

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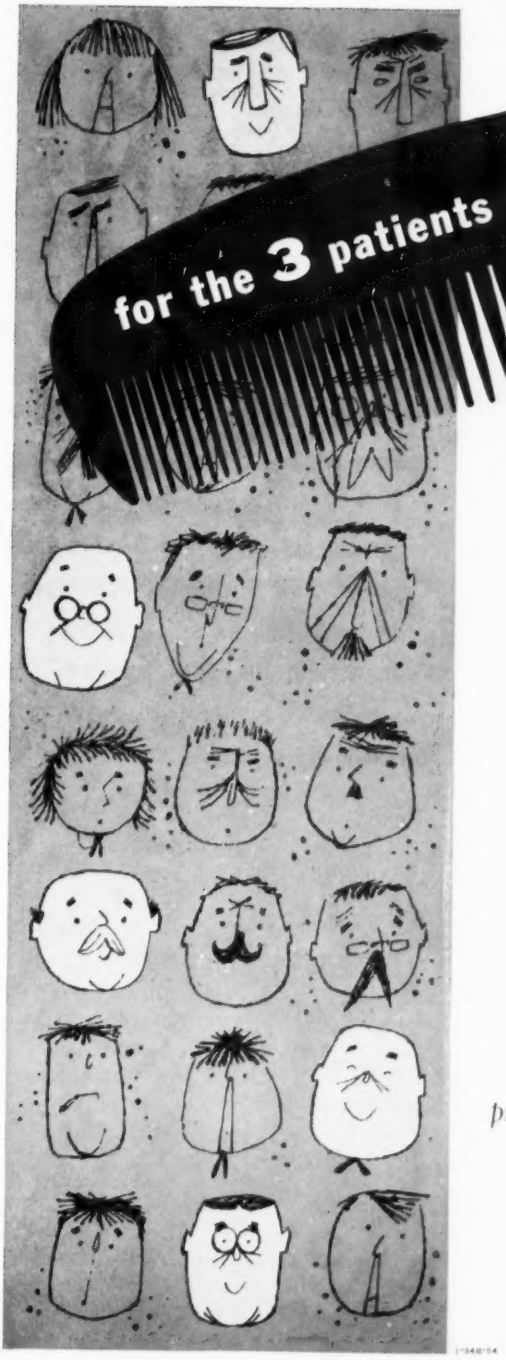

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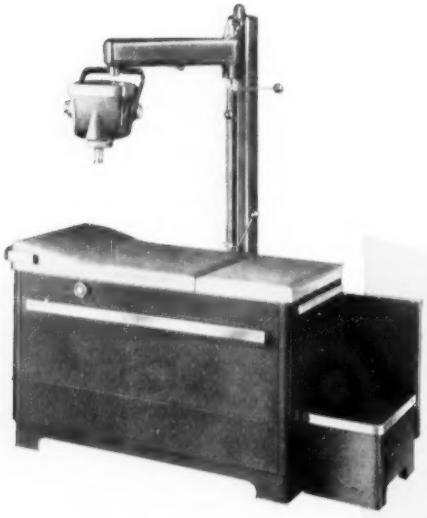

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SULFHYDRYL GROUPS AND DISULFIDE LINKAGES IN NORMAL AND PATHOLOGICAL KERATINIZATION

E. J. VAN SCOTT, M.D.
BETHESDA, MD.
AND
PETER FLESCH, M.D., Ph.D.
PHILADELPHIA

KERATINIZATION is one of the most important metabolic functions of the epidermis. Although numerous investigators have studied the nature of the changes which the proteins of the living cells of the Malpighian layer undergo during the transition to keratinized structures, the exact chemical features of this transformation remain elusive.

One of the most characteristic chemical changes in keratinization involves the sulfur-containing amino acids. Most of the sulfur in keratin occurs in the form of cystine; the disulfide bridges of cystine account for much of the stability and chemical resistance of keratin.

The disulfide bridges in keratin have been generally assumed to result from the oxidation of the sulfhydryl groups of cysteine, found in the stratum Malpighii as follows:

$$2\text{–SH} \xrightarrow{\text{O}} \text{–S–S–} + \text{H}_2\text{O}$$

This view was based largely on histochemical evidence. When sections of the epidermis were stained with sodium nitroprusside, a histochemical sulfhydryl reagent, only the cells of the Malpighian layer stained; there was no reaction in fully keratinized structures, such as the stratum corneum or hair.* The assumption has been made that the disappearance of sulfhydryl groups in finished horny products indicated their conversion to disulfide bridges in both types of keratins, the "hard" and "soft" varieties alike.

This division of the keratins into two types has been made primarily on the basis of their physical properties and sulfur metabolism. The soft keratins desquamate continually or fragment easily, while the hard keratins form rigid, nondesquamating structures. In man, the main representatives of the soft keratins are the epidermal keratin and the medulla of the hair shaft, while the hard keratins comprise the nails and the cortex of the hair. From the standpoint of sulfur metabolism, the soft keratins have been characterized by a low sulfur content and by an identical concen-

This study was supported by Grant No. G-3601 from the United States Public Health Service.

From the Department of Dermatology, University of Pennsylvania (Donald M. Pillsbury, M.D., Director) and the National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare (Dr. Van Scott).

* References 1 to 3.

tration of sulfur in the matrix cells and the horny structures. Chemical data of this nature were based largely on analyses of the horse burr, a rudimentary horny structure on the inner side of the horse's leg.[4] The hard keratins have been generally considered as having a high sulfur content; this sulfur was higher than in the matrix cells from which the hard keratins originated. Thus, hard keratinization was believed to be characterized by an enrichment in sulfur.[5] In both types of keratinization the conversion of the sulfhydryl groups of the living cells of the matrix layers to the disulfide bridges of the keratin structure was accepted as a well-established fact.

Recently a number of observations have been made which question the absolute validity of some of these concepts. With modern histochemical sulfhydryl stains the constant presence of sulfhydryl groups in the stratum corneum was demonstrated.† Moreover, with direct chemical methods, significant amounts of sulfhydryl could be shown also in epidermal scales and other horny structures.[9] These observations have brought forth some controversy regarding the fate of sulfur during keratinization and have suggested the need for systematic determinations of sulfhydryl groups and disulfide linkages in horny structures and in their matrix layers, as pointed out in a recent review.[10]

The purpose of the present work is therefore to shed more light on the nature of sulfur metabolism in keratinization. In order to settle the problem, whether or not during keratinization there is a conversion of sulfhydryl groups to disulfide bridges, these constituents were determined in horny structures of man and animals, and, whenever possible, in the matrix layers from which these structures arose. Since practically nothing is known about the chemical differences between normal and abnormal keratinization, the first steps were taken in this direction by determination of the sulfhydryl and disulfide content of pathological horny layers. Finally, the problem of the basic nature of soft and hard keratinization was reinvestigated, and in the light of these findings previous concepts have been reanalyzed.

MATERIALS AND METHODS

I. *Tissues Analyzed.*—Plantar keratin was obtained by scraping the soles of normal healthy men and women with a sharp knife blade; another source was from large calluses removed from plantar surfaces of healthy adults; a third type was keratin scraped from the sole of an amputated leg.

Pathologic keratin was collected from patients with various skin diseases by removing scales and surface keratin.

Human epidermis was obtained from abdominal skin procured at autopsy and was separated from the corium by stretching.[11] In order to study epidermal layers more closely, human plantar skin from amputated legs was divided according to the following procedure: After removal of the subcutaneous fat, the skin was cut into squares approximately 1.5 by 1.5 cm. These squares were flattened with pressure, frozen in this state, and immediately sectioned into layers parallel to the surface. Each section was 50 to 75 μ thick, and a portion of each was examined microscopically to determine its histologic nature by direct staining of the fresh tissue with hematoxylin. Sections of similar composition were pooled to provide enough tissue for several determinations.

A new method for a possible separation of some of the epidermal components has also been developed in the course of this work. Pulverized, dried epidermis was suspended in ether and centrifuged. The heaviest, more pigmented particles settled to the bottom of the tube, while the superficial layers were lighter colored. Details of this method will be reported elsewhere.

† References 6 to 8.

Horn and hoof from autopsy material was scraped with a sharp knife and the shavings were collected. Horse burr,‡ obtained at autopsy, was frozen and, by manual sectioning, the keratin layer was separated from the Malpighian layer.

All tissues were finely pulverized in a porcelain mortar and dried to constant weight. The powder was sifted through a No. 60 wire mesh to insure uniform particle size and was defatted by washing three times with dry ether.

We also attempted to show whether or not the drying of the powdered tissues, as used by us in the preparation of the specimens before their analyses, had an effect on their sulfhydryl content. To this end, the following experiment was carried out: Immediately after their separation, samples of fresh abdominal epidermis were divided into two parts and weighed. One part was homogenized in 20 parts of water. The sulfhydryl content of an aliquot of this suspension was determined in both the aqueous and the sodium lauryl sulfate (Duponol) extractable forms, as will be described below. The second half was dried, defatted and weighed again. In this way we could estimate the fat and water content of the first sample. Then the second (dried) sample was pulverized and its sulfhydryl content was estimated. Determinations were also carried out at weekly intervals on the same specimen of dried epidermal powder, in order to ascertain whether or not storage had any effect on the sulfhydryl and disulfide contents of the tissue.

II. *Analytical Methods.*—1. Sulfhydryl Determinations: Sulfhydryl was determined under two conditions with Bennett's reagent[12] using 4- to 50-mg. samples of powdered tissue: A. "Aqueous sulfhydryl" values were obtained after incubating the powdered tissue samples with 0.5 cc. of distilled water at 40 C. for one hour. The reagent was added directly to this suspension and therefore the values represent both water-extractable and protein-bound sulfhydryl. B. "Potentially reactive sulfhydryl" was determined after incubating the powdered tissues in a water bath at 40 C. for 1 hour, or in a boiling water bath for 10 minutes, with 0.5 cc. of a 10% solution of sodium lauryl sulfate (Duponol C), similar results being obtained with either type of incubation. Here again the reagent was added directly to the suspension. In all powdered tissues, treatment with sodium lauryl sulfate increased the number of reactive sulfhydryl groups. This increase, which occurs also with other detergents,[9] is part of a denaturing process.[13] The exact nature of the physicochemical changes accompanying this phenomenon is not known, but it is reasonably certain that already existent sulfhydryl groups are made available by this treatment. It does not appear that new sulfhydryl groups are formed by the splitting of disulfide linkages. The following evidence was obtained in support of this assumption: (*a*) Boiling of cystine with sodium lauryl sulfate liberated no measurable sulfhydryl. (*b*) Boiling insulin, a protein wherein all the sulfur is in the form of disulfide, again yielded no measurable sulfhydryl groups. (*c*) When powdered keratin was incubated with 0.05 M iodoacetate, then washed repeatedly with water, and thereafter boiled with sodium lauryl sulfate, the appearance of reactive sulfhydryl groups was completely abolished. This appearance was not interfered with when control keratin samples were similarly treated with 0.05 M acetic acid. (*d*) Boiling keratin samples with 55% lithium bromide, a known hydrogen-bond breaker,[14] resulted in the same sulfhydryl values as obtained with sodium lauryl sulfate. The same was true with 6 M urea. However, both lithium bromide and urea gave less consistent results with the sulfhydryl reagent employed than did sodium lauryl sulfate.

In order to have the results obtained with Bennett's reagent checked with an independent method, a new technique was devised for sulfhydryl determination. While Bennett's reagent combines with water-soluble and water-insoluble sulfhydryl groups alike through mercaptide formation, the new method makes use of a disulfide compound, developed by Barnett and Seligman for the histochemical demonstration of protein-bound, water-insoluble sulfhydryl groups. The reagent oxidizes these groups and in turn, becomes reduced. The split products formed in this process then combine with the sulfhydryl groups of the tissues. For the detailed chemistry,

‡ All animal tissues were acquired through courtesy of Dr. Frantisek Kral, Associate Professor, University of Pennsylvania, School of Veterinary Medicine.

the reader is referred to the original papers of Barrnett and Seligman.§ Details of the adaptation of the Barrnett-Seligman method for the direct quantitative estimation of protein-bound, water-insoluble sulfhydryl groups will be reported elsewhere.

2. Estimation of Disulfide Linkages: Disulfide bonds were estimated after reducing them to sulfhydryl by incubation in a boiling water bath with 2 M potassium cyanide in 0.1 N sodium hydroxide until the keratin particles were dissolved and a clear solution was obtained. The time required for dissolution was 30 to 45 minutes. The reliability of this procedure was ascertained by determining the disulfide content of insulin in identical manner. A 3.4% concentration of sulfur, as disulfide, was found, the same as that reported in the literature.[16] Similarly, disulfide values for hair, horn, nails, and epidermal scales were in agreement with data of previous investigators.[17]

All sulfhydryl and disulfide determinations were done in duplicate or triplicate and results agreed within a 10% range.

RESULTS

1. *Sulfhydryl and Disulfide in Normal Epidermal Keratinization.*—Sulfhydryl and disulfide values of normal plantar keratin are listed in Table 1. These values

TABLE 1.—*Sulfhydryl and Disulfide in Normal Plantar Keratin*

Specimen	Immediately Reactive −SH*	Duponol † −SH	% S as −SH	% S as −SH + S−S	% S as S−S
A	15	50	0.016	0.385	0.369
B	17	55	0.018	0.350	0.332
C	11	36	0.012	0.344	0.332
D	15	50	0.016	0.377	0.361
E	14	50	0.016	0.320	0.304
F	13	52	0.017	0.370	0.353
Average	14	49	0.016	0.358	0.342

* −SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.
† Sodium lauryl sulfate.

are considerably higher than those previously reported for plantar keratin,[7] due in part to a slightly modified method for determination of sulfhydryl and in part to the more thorough pulverization of the keratin in the present work. It can be seen that the values obtained for the different specimens are very similar, irrespective of the source of the keratin.

The sulfhydryl and disulfide contents of successive layers of human plantar skin are shown in Table *2*. Good agreement was found between the values obtained for the comparable layers of the specimens. The amounts of aqueous and Duponol sulfhydryl progressively increase in successive, deeper layers until the corium is reached, and would appear to be proportional to the extent to which cells from the Malpighian layer are included in the analyzed tissues. There is no significant difference in the disulfide content of the various layers until the corium is reached, at which point the disulfide content falls.

In order to check these results, the sulfhydryl and disulfide values of total plantar epidermis were determined and compared with the computed average values of these groups in the combined layers. These two sets of data were in the same range. On the other hand, the sulfhydryl and disulfide content of the corium was negligible (Table *2*). These relationships are schematically illustrated in Figure 1.

§ References 7 and 15.

TABLE 2.—*Sulfhydryl and Disulfide Contents of Successive Layers of Human Plantar Skin*

Specimen and Layers	Estimated Content of Layer	Aqueous —SH *	Duponol SH	% S as SH	% S as SH + S–S	% S as S–S
Specimen A						
Layer 1	Keratin	14	50	0.016	0.385	0.369
Layer 2	Keratin	27	66	0.021	0.362	0.341
Layer 3	7/8 Keratin 1/8 Malpighian L.	24	102	0.033	0.390	0.357
Layer 4	1/2 Keratin 1/2 Malpighian L.	27	129	0.041	0.425	0.384
Layer 5	1/3 Keratin 2/3 Malpighian L.	49	153	0.049	0.410	0.361
Layer 6	1/8 Keratin 3/4 Malpighian L. 1/8 Corium	..	305	0.098	0.415	0.317
Layer 7	1/4 Malpighian L. 3/4 Corium	..	..	.....	0.260	.....
Specimen B						
Layer 1	Keratin	13	52	0.017	0.370	0.353
Layer 2	Keratin	22	64	0.020	0.325	0.305
Layer 3	3/5 Keratin 1/5 Malpighian L. 1/5 Keratin	19	115	0.037	0.354	0.317
Layer 4	1/2 Malpighian L. 1/2 Corium	..	..	.....	0.260	.....
Av. of Specimen A + Specimen B		24	115	0.037	0.364	0.327
Specimen C	Total epidermis	25	88	0.028	0.369	0.341
	Corium	0	7	0.002	0.035	0.033

* —SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

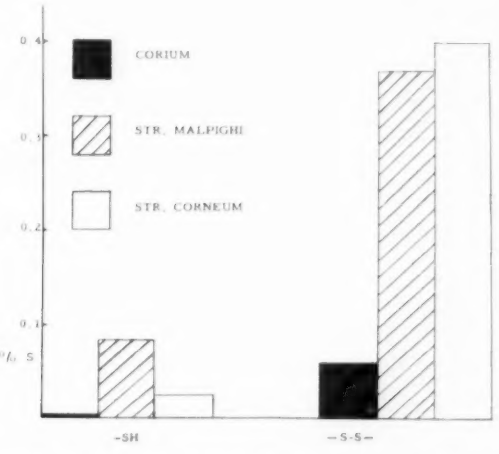

Fig. 1.—Approximate relative amounts of sulfhydryl groups and disulfide bonds in human corium and epidermis.

Table 3 records the sulfhydryl and disulfide content of total epidermis of abdominal skin. In contrast to plantar epidermis, where a greater proportion of the mass is made up of stratum corneum, the epidermis of abdominal skin consists

TABLE 3.—*Sulfhydryl and Disulfide in Normal Abdominal Epidermis*

Tissue	Immediately Reactive —SH * (mM × 10^{-2}/100 Gm.)	Sodium Lauryl Sulfate (mM × 10^{-2}/100 Gm.)	% S as —SH	% S as —SH + S–S	% S as S–S
White epidermis A	45	155	0.050	0.381	0.331
White epidermis B	..	...	.....	0.345	.....
White epidermis C	95	122	0.039	0.470	0.431
White epidermis D	174	326	0.101	0.459	0.358
White epidermis E	44	115	0.037	0.407	0.370
White epidermis F	..	...	.....	0.448	.....
White epidermis G	55	130	0.042	0.490	0.448
White epidermis H	45	143	0.046	0.557	0.511
White epidermis I	68	270	0.086	0.538	0.452
White epidermis J	78	256	0.082	0.512	0.430
Negro epidermis K	15	172	0.055	0.509	0.454
Negro epidermis L	24	185	0.059	0.435	0.376
Negro epidermis M	15	171	0.055	0.457	0.402
Average	59	186	0.060	0.462	0.402

* —SH expressed as mM × 10^{-2}/100 gm. dry weight measure.

TABLE 4.—*Sulfhydryl and Disulfide in Scales from Exfoliative Dermatitis*

Disease	Immediately Reactive —SH *	Duponol —SH	% S as —SH	% S as —SH + —S–S—	% S as —S–S—
Psoriasis	47	220	0.070	0.465	0.395
Psoriasis	100	209	0.067	0.450	0.383
Psoriasis	69	221	0.071	0.420	0.349
Psoriasis	114	129	0.041	0.451	0.410
Idiopathic	68	263	0.084	0.490	0.406
Average	80	208	0.067	0.455	0.388

* —SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

TABLE 5.—*Sulfhydryl and Disulfide in Scales from Ichthyosis*

Subject	Immediately Reactive —SH *	Duponol —SH	% S as —SH	% S as —SH + —S–S—	% S as —S–S—
A (white)	11	53	0.017	0.310	0.293
B (white)	8	82	0.026	0.496	0.470
C (Negro)	19	83	0.027	0.360	0.333
Average	13	73	0.023	0.389	0.365

* —SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

mainly of Malpighian layer. Correspondingly, the sulfhydryl values obtained for the epidermis of abdominal skin are in the same range as those of the lower layers of the plantar skin. (Compare with Layer 5 of Specimen *A*, Table 2.)

Drying and storage had no effect on the sulfhydryl and disulfide contents of the epidermal powder.

2. Sulfhydryl and Disulfide in Pathologic Keratinization.—Sulfhydryl and disulfide values in pathologic keratins are listed in Tables 4 to 6. The most conspicuous

TABLE 6.—*Sulfhydryl and Disulfide in Pathological Keratins*

Disease	Immediately Reactive –SH *	Duponol –SH	% S as –SH	% S as –SH + –S–S–	% S as –S–S–
A. Pathological Plantar Keratin					
Exfoliative dermatitis (due to Mercurial Diuretic)	10	65	0.021	0.617	0.596
T. rubrum infection	17	54	0.017	0.390	0.373
Arsenical keratoses	10	28	0.009	0.440	0.431
B. Keratin from Miscellaneous Skin Diseases					
Scales (dermatitis venenata)	29	99	0.032	0.481	0.449
Epidermodysplasia verruciformis	71	73	0.023	0.538	0.515

* –SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

TABLE 7.—*Sulfhydryl and Disulfide in Human Hard Keratin*

Tissue	Immediately Reactive –SH *	Duponol –SH	% S as –SH	% S as –SH + –S–S–	% S as –S–S–
Hair	6	11	0.0636	5.7	5.7
Nails	9	146	0.047	3.46	3.41

* –SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

TABLE 8.—*Sulfhydryl and Disulfide in Animal Hard Keratins*

Tissue	Immediately Reactive –SH *	Duponol –SH	% S as –SH	% S as –SH + –S–S–	% S as –S–S–
A. Cow hoof	67	230	0.074	5.5	5.4
Plantar surface of cow hoof	11	34	0.012	2.21	2.20
Malpighian layer of plantar surface	..	57	0.018	0.378	0.360
B. Cow hoof					
From vestigial accessory toe	32	155	0.050	4.57	4.52
Plantar surface of vestigial toe	14	226	0.072	1.57	1.50
C. Cow horn					
Deep layers	..	229	0.073	4.16	4.09
Superficial layers	41	112	0.036	1.71	1.67

* –SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

TABLE 9.—*Sulfhydryl and Disulfide in Horse Burr*

Specimen	Immediately Reactive –SH *	Duponol –SH	% S as –SH	% S as –SH + –S–S	% S as –S–S
Keratin	9	82	0.026	0.331	0.305
Malpighian layer	224	590	0.189	0.287	0.098

* –SH expressed as mM × 10^{-2}/100 gm. dry weight tissue.

findings are consistently high sulfhydryl values in scales from patients with psoriasis (Table 4). On the other hand, scales from patients with ichthyosis show no abnormality in their sulfur distribution (Table 5). Sulfhydryl and disulfide values in scales from other keratinizing anomalies are shown in Table 6.

3. *Sulfhydryl and Disulfide in "Hard" Keratinization.*—Sulfhydryl and disulfide values in human hard keratins are shown in Table 7.

In cow's horn the superficial layers had less disulfide and sulfhydryl than the deeper layers. The plantar surface of the hoof and third toe of the cow contains considerably less disulfide than the dorsal surface of the same organs. While the hoof has a relatively high sulfur content, its Malpighian layer contains about as much sulfur as human epidermis. Hence, there is considerable enrichment in sulfur in this structure as the cells proceed toward keratinization (Table 8). This finding is in agreement with those of previous authors.‖

4. *Sulfhydryl and Disulfide in the Horse Burr.*—The sulfhydryl and disulfide values found in the keratin and Malpighian layer of the horse burr are recorded in Table 9. It can be seen that sulfhydryl values in the Malpighian layer of the horse burr are much higher than in any layer of human skin. Also, there is a threefold increase of the disulfide content of the keratin layer over that of the Malpighian layer, a phenomenon which was not found to occur in normal human skin.

COMMENT

1. *Normal Epidermal Keratinization.*—One of the most interesting findings of this study is that, in human skin the disulfide values of the stratum corneum are essentially the same as those of the Malpighian layer. In other words, the cystine content of these two layers is of the same magnitude. The only cystine values in the Malpighian layer reported in the literature are those of animals. Thus in the mouse epidermis 1.5% cystine was found,[19] a value corresponding to the amount of disulfide found by us in human epidermis. The cystine content of the cow's nose was also in a high range.[20] In contrast to the disulfide, the sulfhydryl values in the Malpighian layer are relatively small, amounting at most to only about 25% of the "total" (–SH + –S–S–) sulfur.¶ The fact that there is practically an identical disulfide concentration in the human stratum corneum and stratum Malpighii suggests that a substance, formed already at the level of the Malpighian layer, gives rise directly to the keratinous substance of the horny layer. Our data thus give strong chemical support to the theory that human epidermal keratinization starts in the depth of the Malpighian layer.[10] As early as 1937, Derksen and his co-workers postulated that, on the basis of cystine content and x-ray diffraction pattern, the tonofibrils in the Malpighian layer of the cow's nose were identical with the fibrils of the horny layer.[21] Evidence for the existence of an alpha-keratin pattern in the epidermal proteins of the cow's nose was also presented by Rudall.[22] Our present work extends these findings to normal human epidermal keratinization.

The existence of higher sulfhydryl levels in the stratum Malpighii, as compared with the levels in the stratum corneum, may be merely a reflection of the cellular

‖ References 5 and 8.

¶ Our values represent only a part of the sulfur content, as methionine determinations were not carried out.

metabolism of the rete cells, due in part perhaps to the presence of enzyme systems which require this grouping and which are known to exist in the epidermis. Another possible function of these groups may be inhibition of pigment formation.#

Equally interesting is the relatively high sulfhydryl content of epidermal keratins. If epidermal keratinization were characterized by a conversion of sulfhydryl to disulfide, this process would be incomplete, since 17 to 25% of the sulfhydryl groups of the Malpighian layer escape this conversion.

The differences between the previously held and newly proposed concepts of sulfur metabolism in epidermal keratinization are schematically illustrated in Fig. 2.

In view of the presence of significant quantities of sulfhydryl groups in epidermal keratins, the question of how reactive these groups are must be raised. The great affinity of keratin for arsenic from external sources (such as postmortal uptake by keratinized structures) could be well explained by a reaction between the metal and the sulfhydryl groups of keratin. Whether or not therapeutic measures which influence keratinization may in some instances also cause alterations in the horny layer

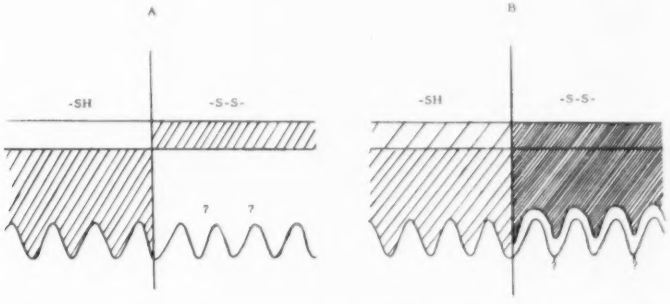

Fig. 2.—Previous authors' and our concepts of relative distribution of sulfhydryl groups and disulfide bonds in epidermis. *A*, previous concept: sulfhydryl limited to Malpighian layer, disulfide to stratum corneum. *B*, present concept: sulfhydryl present in diminished, but significant amounts, in horny layer; disulfide concentration identical throughout entire thickness of epidermis. The possible conversion of sulfhydryl to disulfide in the zone of the basal cell layer cannot be ruled out.

by reacting with the sulfhydryl groups in the keratin molecule, remains the subject for future investigations.

2. *Pathological Keratinization.*—High sulfhydryl values in psoriatic scales have been reported by Zingsheim.[26] This increase in sulfhydryl, however, is apparently not pathognomonic for psoriasis, as it occurs in exfoliative dermatitis from other causes as well. In another type of hyperkeratosis, namely, ichthyosis, the sulfhydryl values in the horny scales are normal. These findings support Rothman's view on the differences between these two forms of keratinization: In psoriasis, the rate of keratin production is accelerated (hence histologically the parakeratosis and chemically the preserved sulfhydryl groups in the scales); in ichthyosis the rate of keratin formation is normal, but the scales, for some unknown reason, have an increased adherence to the underlying epidermal layers and their accumulation gives rise to hyperkeratosis.*

References 23 to 25.

* References 27 and 28.

If epidermal keratinization starts in the depth of the Malpighian layer, chemical changes in diseases like psoriasis may be reflected already at that level. Determinations of sulfhydryl and disulfide in the Malpighian layer of psoriatics would be of great value in our understanding of the nature of the disease process. Unfortunately, such studies are handicapped by the difficulty of obtaining enough tissue for chemical determinations.

3. *Keratinization of the Horse Burr.*—The horse burr has played an important historical role in the development of theories of keratinization. Previous concepts of sulfur metabolism in human epidermal keratinization have been based largely on the sulfur determinations carried out in various layers of this organ. The reported sulfur values in the stratum Malpighii (0.59%) and stratum corneum (0.50%)

Fig. 3.—Cross section of horse burr. Enlarged about 11 ×.

of the horse burr were essentially identical †; since they include methionine sulfur, they are higher than the combined disulfide-sulfhydryl values found by us. In the absence of chemical determinations of sulfur in normal human epidermis, the assumption has been made that keratin of horse burr represented a prototype of "soft" epidermal keratin and that the findings could be directly correlated to human epidermal keratinization.

In order to examine the validity of this assumption, we present a brief description of the horse burr at this point. Horse burr (also called the chestnut of the horse) is a rather firm keratinous structure situated on the inner aspect of the horse's leg. It is a rudimentary toe. Keratin formation in this structure has a morphological pattern analogous to that found for the very hard keratin of the

† References 4, 5, and 18.

horse's hoof ‡ and is quite different in many respects from that occurring in human epidermis. The Malpighian layer is very thick and even with the naked eye one can readily distinguish the various epidermal layers (Fig. 3). The rete cells are closely packed without intercellular bridges and their general direction is an "ascending" one, i. e., at a right angle to the surface of the skin (Fig. 4). These two features will be discussed below in greater detail.

Phylogenetically the horse burr is related to hard keratins, while anatomically and histologically it would appear to occupy a position intermediate between hoof and skin. In brief, horse burr is a specialized structure which has the characteristics of both "hard" and "soft" keratins. Serious objections may be raised when, from

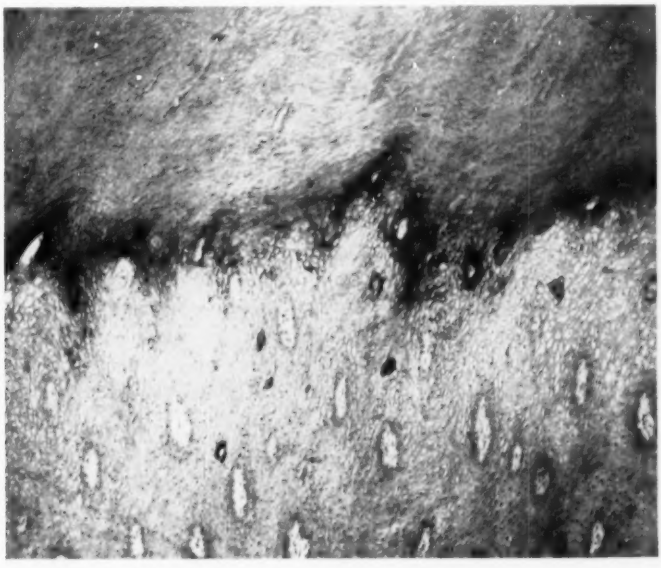

Fig. 4.—Cross section of horse burr. Enlarged about 60 ×. Cells closely packed and at right angles to surface.

such a unique and isolated organ, generalized conclusions are drawn regarding human epidermal keratinization.

Our own data on sulfur metabolism in the horse burr are not at variance with the chemical data of previous workers, who found no difference between total sulfur concentrations of the stratum Malpighii and the stratum corneum. We have found that the combined sulfhydryl-disulfide sulfur of these two layers is essentially the same. There is, however, one important chemical difference between these two layers of the horse burr which heretofore has not emerged and which is revealed by our data: The disulfide content of the stratum corneum is threefold that of the stratum Malpighii. An analogous pattern of increased disulfide content of the stratum corneum over that of the stratum Malpighii has been observed in hard

‡ References 29 and 30.

keratins and seems to be characteristic for this type of keratinization. On the other hand, no specimen of normal human epidermal keratin contained more disulfide than its parent Malpighian layer.

4. *Sulfur Metabolism in Hard Keratinization and Differences Between Soft and Hard Keratins.*—On the basis of histochemical observations it has been claimed that the following criteria distinguish the sulfur metabolism of hard keratinization from that of soft keratinization:

(*a*) The presence of a so-called keratogenous zone. In this narrow, band-like zone at the border between cornified and living cells the sulfhydryl reaction is greatly accentuated.[18] However, both with the nitroprusside stain[31] and with the more modern stain,§ this zone has been observed to occur in epidermal keratin formation as well. Therefore this zone cannot be considered to be characteristic of hard keratinization only.

(*b*) Enrichment in sulfur in the course of hard keratinization.[18] This one criterion appears to be generally valid for hard keratinization. However, instead of a rigid chemical distinction being made between soft and hard keratins on this basis, it would seem rather that these terms represent the two extremes of a series which contains keratins of transitional types. Thus, at one extreme of this series is cow's hoof with a very high disulfide content, amounting to a fifteenfold increase over that of its parent Malpighian layer. Near the middle of the series is the plantar surface of the cow's hoof, physically also very hard, but with a disulfide content approximately one-half that of the dorsal portion of the hoof; this disulfide content represents a sixfold increase over that of the underlying Malpighian layer.‖ Farther toward the opposite end of the series, the keratin layer of the horse burr has a low disulfide content, only three times as high as that of its parent Malpighian layer. The keratin on the surface of the human skin has a low disulfide content, which is identical with that of its Malpighian layer.

On the basis of our studies we believe that one of the features of sulfur metabolism which distinguishes hard keratins from soft keratins is the increase in cystine content in the course of keratinization. Hard keratins were invariably found to contain more disulfide than the matrix cells from which they originated. Disulfide bridges in epidermal structures are indicative of the presence of fibrous structures. One may speculate, therefore, the fibrous precursor of keratin which is present in the form of tonofibrils and intercellular bridges, would make its appearance only late in the course of hard keratinization, while in soft keratinization such fibrous structures would be distributed throughout the entire thickness of the Malpighian layer. This is indeed the case. Thus in the matrix of the hair, the cells are closely packed and no intercellular bridges are visible. The tonofibrils appear only in the upper part of the hair root.[18] The lack of intercellular bridges in the horse burr has been mentioned previously.

Another feature which might be characteristic of hard keratinization is the direction of the keratinizing cells. In epidermal keratinization the cells flatten out

§ References 6 and 8.

‖ The lower cystine content in the plantar region of the cow's hoof and third toe is of phylogenetic interest. In most animals and in man, the plantar surface produces epidermal keratin (so-called "sole horn") and it is noteworthy that even when the plantar surface has become hard, as in the cow, it retains a lower sulfur content, reminiscent of epidermal keratinization.

parallel to the surface. In many examples of hard keratinization the cells elongate and ascend at a right angle to the surface. This feature is most marked in hairs. The existence of a similar pattern in nails is controversial.[21] The fine longitudinal ridges in the nail plate probably indicate that the nail plate originates from the fusion of cellular columns of the matrix. These rows of cells surge forward at a right angle to the occult margin of the root of the nail.[22]

SUMMARY

The sulfhydryl and disulfide contents of "soft" and "hard" keratins from man and animals were determined. In a few instances similar determinations were carried out in the matrix layers from which the horny structures originated.

Significant amounts of sulfhydryl were found in all types of keratins examined.

While there is a diminution in the sulfhydryl content coincident with keratinization, the disulfide concentration of the stratum corneum remains essentially the same as that of the stratum Malpighii. These findings give strong support to the theory that epidermal keratinization starts in the depth of the Malpighian layer; conversion of sulfhydryl to disulfide does not appear to occur above this depth.

In many types of pathological keratinization the sulfhydryl and disulfide contents of the horny scales deviate from normal. The most pronounced, though apparently not specific, aberration is the greatly increased sulfhydryl content of psoriatic scales, an expression of an increased rate of keratinization. In ichthyosis the sulfhydryl and disulfide values were normal.

The enrichment of sulfur in the course of hard keratinization, as described by previous authors, could be confirmed.

The horse burr, previously considered as a prototype of soft keratins, has many of the chemical and morphological features of hard keratins. In the course of keratin formation in this structure, the disulfide values increase threefold, a feature not observed in human epidermis. Conclusions regarding epidermal keratinization in general, drawn from analyses of the horse burr, are reevaluated.

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SO-CALLED "LIPOMELANOTIC RETICULOSIS" OF PAUTRIER-WORINGER

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PAUTRIER and Woringer in 1932 described a large nodular swelling of the lymph nodes, that occurred in patients with erythrodermas, which they named lipomelanotic reticulosis. It was characterized by foci of reticulocytic proliferation in the basic lymph tissue of the lymph-node cortex. The cortical follicles were in part displaced, whereas the medullary follicles appeared unaffected. The remaining cortical follicles were mostly atrophic, occasionally retaining their original size; hypertrophic follicles rarely appeared. The proliferated reticulum cells were large and had a pale cytoplasm. Mitotic figures were conspicuously absent. Groups of such cells contained fat and melanin. Embedded haphazardly in this reticulum were eosinophiles, lymphocytes, plasma cells, and mast cells.

The authors interpreted their findings as an unspecific reaction of the basic lymph tissue to inflammatory processes involving large portions of the skin, and not as a nosologic entity. Similar observations were repeatedly reported (Laipply, Kocsard, and Obermayer, and Fox). The reporting by various authors of cases which clinically and histologically corresponded to those of Pautrier and Woringer as Brill-Symmers disease (giant follicular lymphoblastoma) with involvement of the skin, resulted in a new and confusing aspect being given to the picture of lipomelanotic reticulosis. As examples of this we cite the cases of Rost, Löblich and Wagner, and possibly, the cases of Combes and Bluefarb that histologically were summarily treated. In the same category also belong the two cases Symmers himself reported and to which Rost later referred. All these reports dealt with patients who developed enlarged lymph nodes during an attack of erythroderma. The reported histology was as follows:

Symmers (1938) observed a proliferation of reticulum cells characterized by its limitation to the lymph node cortex and phagocytosis of fat and melanin. The cortical follicles were atrophic or hypertrophic. Nowhere was there a topographical connection between new-growth reticulum and hyperplastic germinal centers. The reticular tissue lacked mitotic figures and had many eosinophiles and lymphocytes.

Rost also described a reticular proliferation limited to the lymph nodes cortex, that phagocytized fat and melanin. In these cases, as well, the cortical follicles were for the most part atrophic.

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Mr. R. Bersani, Cand. Med., assisted in translating this study into English.

Löblich and Wagner found in their cases a monomorphic granulation tissue with a fibroplastic character, which displaced the lymphatic tissue. This granulation tissue contained many melanin-laden cells.

Randerath and Ulbricht and Keller and Staemmler have recently been emphatically opposed to the identification of these findings with the well-defined and characteristic changes of Brill-Symmers disease. Brill-Symmers disease has been exhaustively investigated, especially its pathologic-anatomical aspect (Brill, Baehr, and Rosenthal; Robb-Smith; Rüttner and von Albertini; von Albertini and Rüttner). It is a tumor-like lymph node affection characterized by follicular hyperplasia, restricted to the germinal center. In 30% of the cases there is also involvement of the spleen. The germinal centers finally break through the surrounding rim of lymphocytes and become confluent. The giant follicles are the result of a neoplastic proliferation of the reticular cells at the expense of the basic lymph tissue. In contrast to lipomelanotic reticulosis there is a complete lack of the inflammatory granulation with eosinophiles and plasma cells. After a latent period of many years, Brill-Symmers disease can become malignant, and the result is a reticulosarcomatosis. For this reason von Albertini and Rüttner classified it as giant follicular lymphoblastoma under the presarcomatous systemic conditions of the lymph system. The differentiation of lipomelanotic reticulosis from Brill-Symmers disease should not cause any trouble. There remains the unusual reticular proliferation first described by Pautrier and Woringer, which poses a few diagnostic and pathogenic questions, as there is in all probability a morphologic connection between it and specific granulomatous lymphadenopathy (Hodgkin's disease, mycosis fungoides). We report on seven cases that were observed and followed up at the Dermatological Clinic, University of Zurich.

REPORT OF CASES

Case 1.—Rudolph Sch., 68-year-old man, for 18 months had a recurring skin condition on the face and arms that finally involved the total integument. At admission, subacute erythroderma with intense erythema of the skin, diffuse infiltration, and lamellar and furfuraceous scales. The skin varied from a deep brown to a dirty slate color. No genital or axillary hair. In the axillary and inguinal regions were lymph nodes that attained plum size, moderately dense, well defined, and indolent. Blood picture: Hb. 86%; RBC 4,200,000; C. I. 1.0; WBC 16,000. Differential: Neutrophiles 49%; band neutrophiles 2%; eosinophiles 24%; mononuclears 4%; lymphocytes 21%. Blood chemistry: normal. Electrophoresis: marked increase of globulin, especially of gamma globulin. Hypoalbuminuria.

Diagnosis: Erythroderma with enlarged axillary and inguinal lymph nodes. Biopsy revealed the following: The epidermis is acanthotic, in some places attaining a thickness several times the norm. The stratum corneum has been practically all shed off in splinters, and, where still present, is parakeratotic. Here and there, especially above the papillae, there is spongiosis without pronounced blister formation. The interpapillary ridges are both thickened and thinned, the papilla itself is occasionally elongated and at times edematous. Where the edema is not pronounced, there is a loose infiltration of lymphocytes and fixed cells. The infiltration occurs most strongly in the subpapillary layer, occasionally about the stratum reticulare as well. The infiltrate is of a varying nature that consists of lymphocytes and numerous histiocytic elements. Eosinophiles and neutrophiles are not present, and plasma cells rarely occur. Histologic diagnosis: Eczematous dermatosis with a somewhat granulomatous appearance of the infiltrates.

Under treatment with corticotropin (ACTH) and penicillin, the skin lesions healed and the lymph nodes regressed.

Case 2.—Emil St., a 51-year-old man had an exquisite turpentine hypersensitivity with recurrent attacks of eczema during the past 16 years.

At the time of the last hospitalization there was a widespread, exudative erythroderma-like contact eczema. Enlargement of the lymph nodes in the axillary and inguinal regions. The inguinal nodes were enlarged to plum size and were very painful to touch. However, they were definable from the surroundings. Blood picture: Hb. 81%; RBC 4,000,000; C. I. 1.0; WBC 14,000. Differential neutrophiles 63%; band neutrophiles 4%; eosinophiles 3%; mononuclears 10%; lymphocytes 19%; plasma cells 1%. Blood chemistry: total protein 5.7%; otherwise normal.

Diagnosis: Generalized contact eczema (turpentine) with enlargement of the axillary and inguinal lymph nodes.

After several weeks of bland treatment the skin lesions were practically healed. The lymph nodes regressed.

Case 3.—Paul Sch., 62-year-old man, had leg eczema of two year's duration, which became generalized. At admission all of the skin was swollen and of a doughy consistency; on the face it was weeping. Pigment transposition in all areas of the skin resulted in symmetrically arranged, palm-sized, depigmented, dirty-slate-colored patches of a map-like configuration. The axillary lymph nodes were cherry-sized; those of the inguinal region were in the plum-sized class, indolent to touch and well defined. The axillary and genital hair was practically all gone. Blood picture: Hb. 87%; RBC 5,100,000; C. I. 1.0; WBC 12,600. Differential: neutrophiles 29%; band neutrophiles 11%; eosinophiles 18%; monouclears 8%; basophiles 1% lymphocytes 28%; plasma cells 5%. Blood chemistry: normal.

Diagnosis: Secondary erythroderma following contact eczema with enlargement of the axillary and inguinal lymph nodes.

The patient died of a heart attack. Necropsy diagnosis: Generalized eczematoid dermatosis. Lipomelanotic reticulosis of the axillary and inguinal lymph nodes. Eccentric hypertrophy of the heart. Obstructive coronary sclerosis. Fibrosis of the myocardium. Changes due to passive chronic congestion in the lungs, liver, and spleen. The mediastinal and retroperitoneal lymph nodes displayed no pathologic changes.

Case 4.—Irene L., 29-year-old woman, six weeks prior to hospital admission had an itching skin lesion which became generalized. At admission, the skin, with the exception of the face, was erythematosquamous and somewhat infiltrated. Arranged in groups were pinhead- and lentil-sized papules with an occasional blister. The pruritus was unbearable. The axillary and inguinal lymph nodes were not enlarged to any great extent, but near the right axilla was a cherry-sized, hard, well-defined lymph node.

Diagnosis: Generalized lichen ruber planus with enlargement of the lymph nodes. The skin biopsy from the right thoracic region revealed the following: The epidermis is thickened, in places doubled or even quadrupled. The ridges are flat, with an occasional dome shape. The stratum corneum is, where still present, composed of thin layers. The stratum granulativum is multilayered. The Malpighian layer appears unchanged except for an occasional zone of liquefaction of the basal layer. The edematous dermal papillae are either compactly or loosely infiltrated with round cells, with the compact areas adjacent to the epidermis. At no place does one see fissuring. There are chromatophores present in some of the dermal papillae. Some of the vessels in the stratum reticulare are surrounded by a layer of infiltrate. Histologic diagnosis: Lichen ruber planus (probable).

Case 5.—Johann Schw., 72-year-old man, had a history of recurring leg eczema and a sensitive skin. Ambulatory treatment over a number of years. Hospitalization because of generalization due to a drug idiosyncrasy. At admission, the skin was covered with epidermal papules occurring in groups or singly, with occasional blisters. The skin was moderately infiltrated and reddened. Enlargement of the lymph nodes in the inguinal folds. Differential blood picture: WBC 9,100; neutrophiles 64%; band neutrophiles 2%; eosinophiles 8%; lymphocytes 26%.

Diagnosis: Generalized eczema with enlargement of the inguinal lymph nodes.

Case 6.—Johann H., 51-year-old man, had chemical burns on the arms and forearms. After months of local treatment, a generalized eczema developed. The skin had an erythroderma-like appearance. Fist-sized lymph node packets in both inguinal folds. Blood picture: WBC 11,300, neutrophiles 58%; band neutrophiles 7%; eosinophiles 2%; monocytes 14%; lymphocytes 19%. Blood chemistry: normal.

Diagnosis: Secondary erythroderma with inguinal lymph node enlargement.

After five months of stationary treatment, the patient was released from the hospital as cured. An ambulatory control six months later showed the skin to be in good condition, and the enlarged lymph nodes had returned to normal size.

CASE 7.—Jakob Z., 51-year-old man, had a year-old hypersensitivity to Thomas slag that resulted in an eczema of the arms, which became generalized and infected. With the generalization of the eczema, the axillary, inguinal, and supraclavicular lymph nodes became enlarged, but indolent, and though fused together were still definable from the surrounding tissue. The blood picture showed a WBC count of 9,000, of which 20% were eosinophiles.

Diagnosis: Generalized, secondary infected eczema with lymph node swelling.

After many months of stationary treatment the skin lesions healed, and the enlarged lymph nodes regressed.

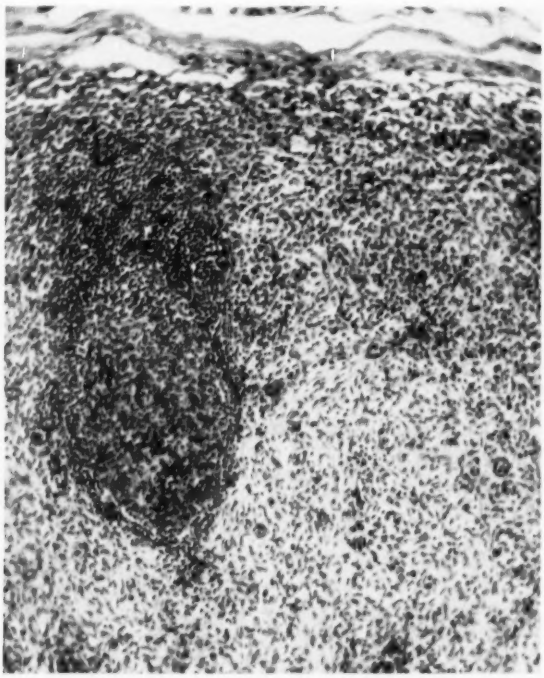

Fig. 1.—Section through cortex of a lymph node with lipomelanotic reticulosis showing an unaffected cortical follicle. H. 139/53 H.E. (×45).

HISTOLOGY OF OUR CASES

Enlarged lymph nodes from all seven cases were excised and histologically examined. All the lymph nodes exhibited basically the same changes. Therefore, a general description follows rather than the individual description of each biopsy.

The fibrous capsule in some of the lymph nodes is slightly thickened; however, in no preparation could we find a periadenitis. In the cortical portion of the basic lymph tissue are cords and fields of tissue composed of pale-staining cells. Only in a few places does this tissue invade the medullar portion of the lymph node. It is possible to find in the same lymph node unaffected as well as pathologic cortex areas. In the affected cortex areas the cortical sinuses are partly intact; however, the cortical follicles are either missing or separated from each other by thick strands of this pale-staining reticular tissue. The remaining cortical nodules are usually atrophic

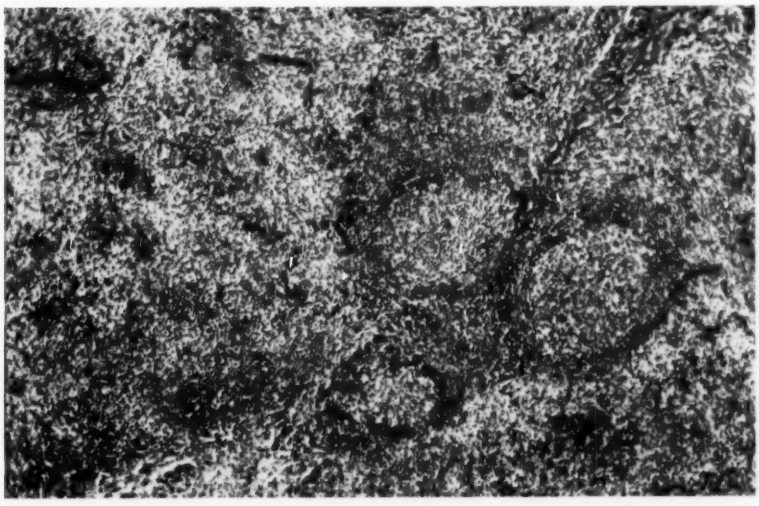

Fig. 2.—Lipomelanotic reticulosis. Low magnification view of a subcortical segment H. 395/53 H.E. (×23)

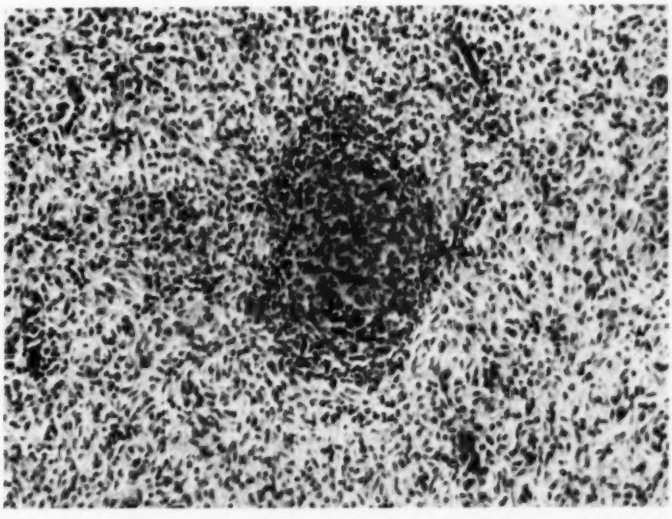

Fig. 3.—Atrophic lymph nodule in midst of lipomelanotic reticulum. Observe the small lymphoid rim of the follicle. H. 139/53 H.E. (×53)

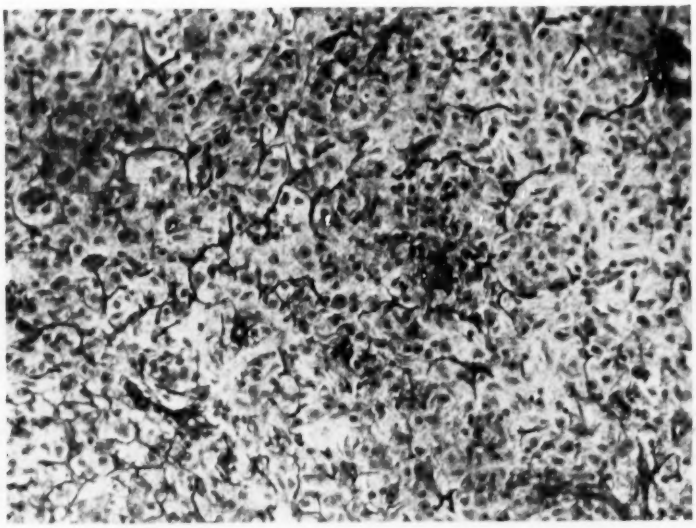

Fig. 4.—Silver-positive fibrillar network of the lipomelanotic reticulum. H. 139/53 Tibor-Papp. (×90)

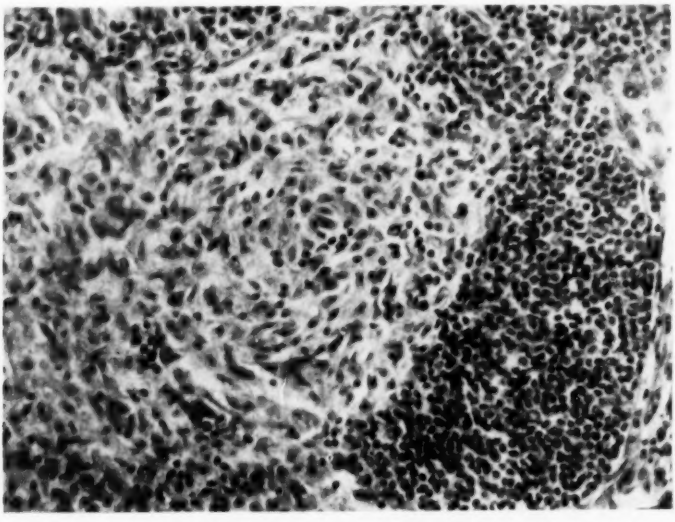

Fig. 5.—Granulomatous lipomelanotic reticulum. The lymphatic tissue is being displaced. H. 139/53 H.E. (×90)

and surrounded by a thin zone of lymphoid tissue. Rarely is this new-growth tissue observed breaking into the medullary sinuses. In our seven cases the germinal centers are at no time the origin of the reticular new growth. The reticular tissue is composed of large, epithelioid reticulum cells with pale-staining cytoplasm. The cell borders are not distinct and appear to overlap. The reticulum cells have large round or oval nuclei. The nuclei seem to have a small amount of chromatin and there are one or two nucleoli. The nucleus-cytoplasm ratio is always in favor of the cytoplasm. The reticulum cells are uniform in appearance, and mitotic figures seldom occur. In large areas the cells appear haphazardly arranged, or they can be grouped together to form granulomatous nodules.

Recently affected lymph nodes have many lymphocytes, plasma cells, and eosinophiles amidst the reticulum cells; in the older lymph nodes they are fewer in number. The eosinophiles are found most often around the granulomatous areas. The reticulum cells are never polymorphic, and Sternberg's giant cells are never present. In fact, giant cells play no role whatsoever in this granulomatosis. The reticulum cells, however, can become quite voluminous by inclusion of large drops of fat. These fatty reticulum cells are encountered in groups, and in a hemalum-eosin preparation are recognizable because of their large vacuoles. There are other fatty cells,

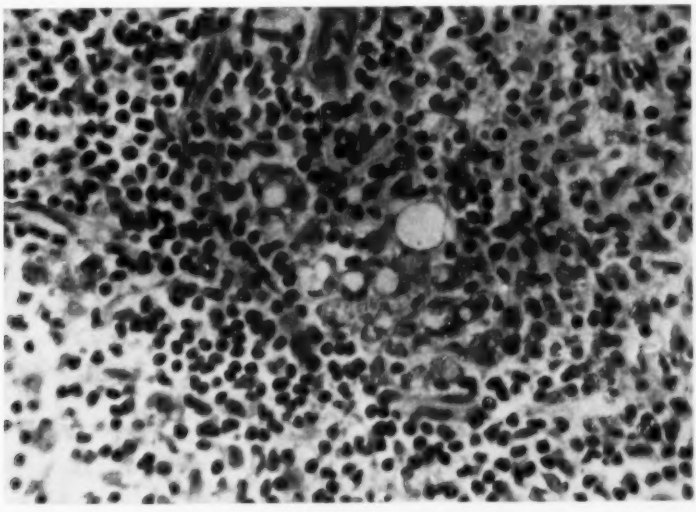

Fig. 6.—Group of fat phagocytizing reticulum cells occurring in lipomelanotic reticulosis. Note the vacuoles. S. 8867/42 H.E. (×180)

not as voluminous, containing droplets of fat with a foamy cytoplasm. These appear usually in the outer portion of the reticular areas. The modus and quantitative fatty involvement, however, can be determined exactly only with the aid of Sudan or scarlet-red staining. In addition to fat, we encounter as inclusions a silver-positive, iron-negative pigment, which must be considered as being mostly melanin. A small amount of iron-positive pigment is occasionally encountered in the new-growth reticulum and in the germinal centers of the remaining cortical nodules. The amount and extent of pigment inclusions seems to be correlated with the length of time of the illness, as we find little or no melanin in the cases with short dermatological histories, and massive intracellular depots in the lymph nodes of patients with long histories. Fat and melanin are often included in the same reticulum cell. The recently affected lymph nodes have many vessels; as the condition becomes older, the number of vessels decreases. Necrosis, fibrosis, or hyalinosis is not a part of the histologic picture in this lymph node condition. The process is characterized by the monotonous and uniform aspect of the tissue configuration. This monomorphic reticular tissue has none of the criteria which distinguish a blastomatous hyperplasia.

The lymph node picture as described above corresponds exactly to the description of the lipomelanotic reticulosis as reported by Pautrier and Woringer in 1932.

HISTOLOGICAL DIFFERENTIAL DIAGNOSIS

There are a number of lymph node affections that are more or less similar to lipomelanotic reticulosis, and we believe a detailed discussion of the distinguishing characteristics is desirable.

Hodgkin's Lymphogranuloma.—The differentiation from an early stage of Hodgkin's lymphogranuloma is most likely to cause difficulty. Both affections are of a reticulogranulomatous character with infiltration of eosinophiles and plasma cells. The lipomelanotic reticulosis does not have the pleomorphism, and Reed-Sternberg giant cells do not occur. The absence of necrosis and fibrosis in lipomelanotic reticulosis will also aid in the differentiation. The absence of Reed-Sternberg cells does not absolutely rule out Hodgkin's disease, and the necrosis and fibrosis are often lacking as well in an early stage. In our opinion, the fatty degeneration and melanin inclusion and the lack of pleomorphism are more satisfactory microscopic criteria in the differentiation from an early stage of Hodgkin's disease. The differentiation from a fully developed case of Hodgkin's disease should not be difficult.

Mycosis Fungoides.—The differentiation from mycosis fungoides is important, because in a great number of cases the clinical picture will suggest mycosis fungoides. Here as well there is histologically a reticular granulation tissue with eosinophiles and plasma cells embedded in the reticulum mesh. The lymph nodes in mycosis fungoides, as in Hodgkin's disease, are totally destroyed, or only remnants remain. In lipomelanotic reticulosis the lymph node changes are restricted to the cortex of the lymph node, and even in the cortex the amount of damage can be variable. The presence of fat and melanin inclusions in the reticulum cells, the absence of pleomorphism and of the typical large, plump, round, or segmented cells with the deep-staining nuclei, which are typical of mycosis fungoides, should make the differentiation a relatively simple matter.

Lymphoreticulose Bénigne d'Inoculation.—In 1950, Debré, Lamy, Jammet ,Costil, and Mozziconacci, and, some weeks later, Mollaret, Reilly, Bastin, and Tournier described *lymphoreticulose bénigne d'inoculation (maladie des griffes de chat),* which in the initial stages displayed a reticular cell new growth, and in later stages tuberculoid nodules and abscesses. Rüttner observed that the initial stage could be similar to an early stage of Hodgkin's disease. If we disregard the fat and melanin inclusions, the lymph nodes of lipomelanotic reticulosis can have a morphologic similarity as well. The events preceding and the clinical course should prevent a false diagnosis. Similar changes occur at times with lymphogranuloma venereum and tularemia, and in the interest of completeness these two diseases are mentioned.

Brill-Symmers Disease (Giant Follicular Lymphoblastoma).—As we have already discussed the histologic differences of Brill-Symmers disease, we shall omit the differential diagnosis at this point.

The separation of sarcomatous degenerated giant follicular lymphoblastoma from lipomelanotic reticulosis is more difficult. In fact, Symmers, Rost, and Löblich and Wagner reported the lymph nodes as being identical in both diseases. Lipomelanotic reticulosis does not have the necessary criteria of a sarcoma (cell and nuclear pleo-

morphism, hyperchromasia, atypical mitotic figures, and vessel invasion). Furthermore, in the sarcomatous degenerated giant follicular lymphoblastoma the sprung follicles are in direct contact with the sarcomatous areas, whereas in lipomelanotic reticulosis the follicles are clearly demarcated from the reticular new growth and even shoved aside by it. In addition, the sarcomatous degenerated Brill-Symmers disease lacks the granulomatous character, the fat and melanin inclusions of the reticulum, and the infiltration with eosinophiles and plasma cells. With careful histologic study neither of these conditions should create too much difficulty.

Does lipomelanotic reticulosis belong to the chronic inflammation hyperplasia group, or to the granulomatous lymph node affections?

The histologic separation of lipomelanotic reticulosis from the specific granulomatous lymph node diseases (Hodgkin's, lymphogranuloma, mycosis fungoides) has been discussed in some detail. Clinically as well, one has the impression that it is not a progressive disease, as the lymph nodes always regress after the skin condition has healed.

It is also distinct from banal lymphadenitis. Here all the components of the affected lymph nodes are enlarged. Only the reticulum of the basic cortical tissue

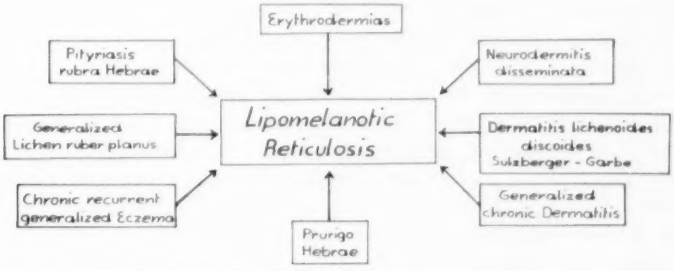

Fig. 7.—Occurrence of lipomelanotic reticulosis.

of the affected lymph node in lipomelanotic reticulosis is involved, and the other tissue elements never display changes in the sense of an inflammatory hyperplasia. Careful analysis of the reticular tissue reveals an inflammatory-granulomatous character resulting from the infiltration of eosinophiles, lymphocytes, and plasma cells, and the abundance of vessels. We believe lipomelanotic reticulosis should be classified under the heading of chronic inflammation hyperplasia. For morphological reasons (granulomatous character) it should be given a special position in that nosologic group.

OCCURRENCE OF LIPOMELANOTIC RETICULOSIS

Pautrier and Woringer considered this lymph node affection as a secondary inflammatory reaction of the superficial lymph nodes in response to an acute or chronic generalized dermatosis. The same lymph node changes occur in such diversified dermatoses, as are illustrated in the accompanying chart.

In our series of cases it occurred three times in erythrodermas subsequent to contact eczemas, and once during erythroderma of unknown etiology. Chronic generalized eczema and generalized lichen ruber planus were the causes in the remaining two cases. Sulzberger, Ramel, and Kocsard found the same lymph node changes in six cases of dermatitis lichenoides discoides (Sulzberger-Garbe), Löblich

and Wagner in chronic dermatitis and neurodermatitis disseminata, Obermayer and Fox, in a case of lichen ruber planus, and Jadassohn, in a case of pityriasis rubra (Hebra). All reported lymph node changes corresponding with those of lipomelanotic reticulosis. It is possible that the prurigo buboes also belong to the group of lipomelanotic reticulosis. These lymph node changes probably occur in other generalized skin diseases as well. In the chart we have included only those diseases in which the lipomelanotic lymph node reticulosis has been histologically verified. Erythrodermas were found most often in the cases of Pautrier and Woringer. In connection with this we must mention a case of erythrodermic mycosis fungoides, the only one we have found in the literature, which Pautrier and Woringer reported in 1939. The first biopsy revealed a classic lipomelanotic reticulosis; the second, a year later, revealed a mycosis fungoides. Therefore the lipomelanotic reticulosis was, in our opinion, an unspecific result of the cutaneous inflammation. The conclusion that lipomelanotic reticulosis belongs to the group of premycotic changes is not justified. However, we can learn from this example that the presence of lipomelanotic reticulosis does not necessarily exclude a concomitant basic disease, for example, mycosis fungoides or malignant granuloma.

One should not be content with a single biopsy, when clinically mycosis fungoides or lymphogranuloma is suspected.

CONCLUSIONS

After due consideration of the clinical picture and course and the pathologic-anatomical findings, we consider lipomelanotic reticulosis, as did Pautrier and Woringer, to be a resorptive, inflammatory reaction of the basic lymph tissue in the superficial lymph nodes as a result of a chronic or acute generalized dermatosis. The lipomelanotic reticulosis occurs not only in primary or secondary erythrodermas, but in any case of generalized dermatosis.

The prerequisites necessary for the formation of this lymph node condition are unknown. It must not be considered simply the result of a reaction to a chronic or acute skin condition. For example, melanin is found in the cortical and intermediary sinuses of chronic inflammation of the lymph node without resulting in any of the morphologic changes encountered in lipomelanotic reticulosis. Melanin and fat inclusions appear simply to be attendant phenomenas of this lymph node reticulosis.

One might believe that the lymph node changes are a result of medications, such as tar or chrysarobin. This pathogenetic possibility is excluded, as we find the identical lymph node changes in untreated erythrodermas. The only remaining hypothesis is that lipomelanotic reticulosis could be caused by still unknown processes of secondary nature occurring in the skin as a result of a widespread dermatosis (release of lymph node stimulating substance?) Lipomelanotic reticulosis is not in itself a complete disease. We are not in agreement with Löblich and Wagner, who called this lymphadenopathy a pigmented lymphogranuloma, thereby creating the impression of a disease entity. Even though there are times when lipomelanotic reticulosis has a superficial resemblance to lymphogranuloma maligna, there is no justification for the labeling of this limited reaction of a lymph node with a name that does not take into consideration the entirely different course of the affection. Names, as Pautrier-Woringer's disease (Keller and Staemmler), reticulohistiocytosis cutanea hyperplastica begnina cum melanodermia (Baccaredda), or reticulo-

histiocytosis cutanea cum melanodermia (Neuhold and Wolfram) are misleading, because they give the connotation of a nosologic entity to the affection. As this is not the case, we think the name lipomelanotic reticulosis first proposed by Pautrier and Woringer is most suitable.

We hope that this lymph node affection, first described in 1932, will regain its original significance after having been described during the last few years as a *morbus sui generis* or identified with giant follicular lymphoblastoma.

SUMMARY

Enlarged lymph nodes occurring in seven patients with extensive skin affections (erythroderma subsequent to contact eczema, erythroderma of unknown etiology, generalized recurrent contact eczema and generalized lichen ruber planus) underwent clinical and pathologic-anatomical investigation. The histologic picture of the lymph nodes showed a granulomatous reticulosis of the basic lymph tissue with inclusions of fat and melanin. The changes were for the most part restricted to the cortex of the lymph node. A discussion of the histology and differential diagnosis from other granulomatous lymph node affections, and differences from giant follicular lymphoblastoma, in particular, were included. The authors' opinion is that the changes are a result of a chronic unspecific reaction of the basic cortical lymph tissue to various inflammatory dermatoses. In support of Pautrier and Woringer, we also have labeled this lymph node affection lipomelanotic reticulosis.

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SOUTH AMERICAN BLASTOMYCOSIS OR PARACOCCIDIOIDOMYCOSIS

The Mycosis of Lutz, Splendore, and Almeida

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LOS ANGELES

DURING the eight years which have elapsed since the subject of South American blastomycosis was last discussed in a publication in English,[1] numerous investigators working in the endemic areas have assembled data which necessitate extensive revision in previously held concepts of its symptomatology, pathology, mycology, and therapy. Although the occurrence of the infection seems to be limited to but a small portion of the globe, the facts known at this time concerning its pathogenesis should be easily available for study by practitioners in other regions as well, lest the search for methods of control of the medical mycoses in general be hampered by lack of awareness of some feature less elusive in this entity than in others. This communication is presented to make this information available in English.

Fig. 1.—Erosive and ulcerated lesions in the mouth are common in South American blastomycosis.

GENERAL SURVEY

Definition.—South American blastomycosis is a progressive, usually fatal, chronic granulomatous disease of the mucous membranes, lungs, lymph nodes, skin, and viscera caused by a single species of fungus, Aleurisma (Blastomyces) brasiliensis.

History.—In 1908, Lutz,* in São Paulo, Brazil, observed two patients with lesions of the oral mucosa, accompanied by cervical lymphadenopathy. He also isolated the causative fungus, described its

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* References 2 and 3.

multiplication by a budding process, and named the disease "pseudo coccidioidal granuloma." Other reports soon followed by Carini [4] and by Splendore † concerning the clinical aspects of the disease and confirming Lutz's observations on the morphology of the fungus.

In subsequent years, numerous papers appeared in the literature,‡ usually suggesting new designations for the fungus and indicating that South American blastomycosis was being confused with Coccidioidomycosis, which had been observed by Posadas [15] and Wernicke [16] in the Argentine in 1892.

Beginning in 1929, Almeida presented a series of papers § in which he studied the mycology, pathology, and symptomatology of South American blastomycosis, contributing decisively to its complete individualization as an entity.

More recently, Bogliolo || and Aroeira Neves [33] have carefully studied the morphology and taxonomy of the causative fungus, presenting several new observations which appear to be convincing and which will be discussed later.

Geographic Distribution.—This mycosis occurs principally in Brazil, particularly in the states of São Paulo, Rio de Janeiro, and Minas Gerais. Almeida and his coworkers [34] reported a total of 750 cases in São Paulo up to 1945. Numerous patients have been observed in Argentina ¶ and a few in other South American countries. No instances of this infection have been reported from other continents.

Incidence.—The following figures are taken from Almeida's review of 750 cases: The disease occurs more frequently in adults, 19.4% in the age group from 41 to 50; 18.9% in the group 21 to 30, and

† References 5 to 9.
‡ References 10 to 14.
§ References 17 to 27.
|| References 28 to 32.
¶ References 35 and 36.

Fig. 2.—Illustrating necrotic destruction of the lips accompanied by papular and crusted lesions.

Fig. 3.—Showing extensive vegetating lesions covered by hemorrhagic crusts.

18.5% in the group 31 to 40. The great majority of patients were men (87.2%). The disease is most prevalent among agricultural workers, apparently because they come in direct contact with vegetative material.

Mode of Infection and Transmission.—The portal of entry is usually the oral mucosa. Agricultural workers habitually clean the teeth with small fragments of wood and frequently chew the stems and leaves of many plants. Although attempts to prove the existence of the fungus on such material by artificial culture methods have not yet been successful, it appears almost certain that the infection is acquired from such an exogenous source.

South American blastomycosis may begin as a dental or peridental granuloma, according to Bogliolo,# and Aleixo and Furtado.[39] It is believed that this explains a small number of cases in which lesions in the cervical lymph nodes were considered to be "primary," the portal of entry being not otherwise apparent. Other sites of inoculation which have been reported occasionally are the tonsils [40] and the conjunctival,[41] nasal,[41] and anal mucosas.* Primary inoculation into the skin is apparently rare, and convincing evidence is difficult to obtain. A few cases of infection originating in the gastrointestinal tract have been reported.† Rarely the infection appears to have started in the larynx or in the lungs.[41] Direct contagion from person to person has not yet been proved.

Once inoculated, the infection is disseminated by both the lymphatic and hematogenous routes and may affect practically all organs eventually.

SYMPTOMATOLOGY

Different symptom complexes occur in South American blastomycosis, dependent on the portal of entry of the fungus. Almeida distinguishes the following clinical types of infection: cutaneous, lymphangitic, visceral, and mixed. Actually, a clear-cut instance of any of the first three types listed is rarely found; usually these forms are combined in various ways. For example, one of the most common clinical types combines lesions in the oral mucosa, cervical lymph nodes, and lungs. Therefore, for clarity of description, we favor the separation suggested by Azulay [41] into "tegumentary" and "extrategumentary" clinical manifestations. (The term "tegumentary" includes mucosal as well as cutaneous lesions.)

I. *Tegumentary Clinical Manifestations.*—The primary lesions are found most often on the mucosal surface of the gums, cheeks, lips, palate, nose, and tongue. They are usually erythematous, ulcerated areas, showing characteristic tiny, yellowish spots interspersed with reddish ones giving a fine granular appearance. This picture was described by de Aguiar Pupo,[47] who named it "mulberry-like erosive stomatitis" (Figs. 1 and 2). Occasionally the lips become swollen sufficiently to justify the descriptive term "proboscis-like lip."

Cutaneous lesions may occur on the skin around the mouth or nose in continuity with the involved mucosa. The skin also becomes affected secondarily by ulceration and fistulization of enlarged lymph nodes, particularly in the cervical region, simulating the picture of scrofuloderma. Cutaneous lesions are also frequently hematogenous in origin. They may be papular, papulopustular, papulotuberous, papilloma-

References 37 and 38.

* References 42 and 43.

† References 44 to 46.

tous, frambesiform, ulcerated and ulcerovegetative (Fig. 3). Such lesions as these may occur in large numbers, usually on the face, but also on the trunk and extremities.

The subcutaneous tissues may be invaded by the extension of mucosal or cutaneous lesions or by the hematogenous route.

II. *Extrategumentary Clinical Manifestations.*—A. Lymph Nodes: Involvement of the lymph nodes, sooner or later in the disease, is one of the most common features of Lutz's mycosis (Fig. 4). The cervical and the submaxillary groups are most commonly affected, becoming involved from lesions in the oral mucosa or in the

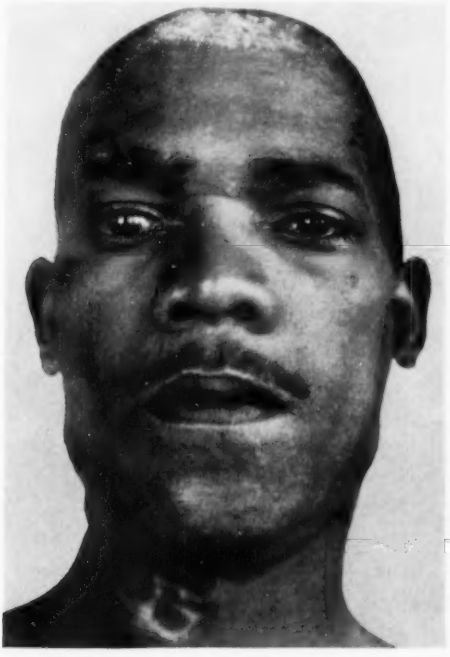

Fig. 4.—South American blastomycosis of the lymphatic type, simulating Hodgkin's disease.

tonsils. Sometimes the presence of enlarged lymph nodes is the only apparent clinical manifestation of the mycosis. The lymphadenopathy may be sufficiently generalized to simulate Hodgkin's disease. Eventually the nodes suppurate and rupture through the skin.

B. Respiratory System: Until recently, pulmonary involvement in South American blastomycosis was considered to be sufficiently rare as to furnish a means of clinical differentiation between that mycosis and North American blastomycosis (Gilchrist's disease).‡ Many authors,§ including one of us (T. A. F.[51]), have shown, however, that the lungs are affected in a high percentage of cases (57 to 94%). The

‡ References 27, 48, and 1.

§ References 49 to 53.

clinical signs show wide variations. The patient may or may not have a cough with purulent sputum, which is occasionally blood streaked. Rales may be audible. However, the signs and symptoms are often mild, contrasting with the severity of the parenchymatous changes revealed by x-ray studies or at autopsy.[55] The roentgenographic aspects include macronodular and micronodular lesions, disseminated or grouped miliary lesions, fibrosis, cavitation and pleural thickening (Fig. 5). The pulmonary picture is by no means diagnostic and should always be differentiated from tuberculosis, which is frequently associated.[49] Lesions in the larynx may produce dysphonia or aphonia.

C. Digestive Tract: The mouth and pharynx are affected in almost every case, the gastrointestinal tract less frequently, and usually only secondarily to other manifestations of the disease. It may happen, however, that the gastrointestinal process is the primary one and remains the only manifestation of the mycosis. In such a

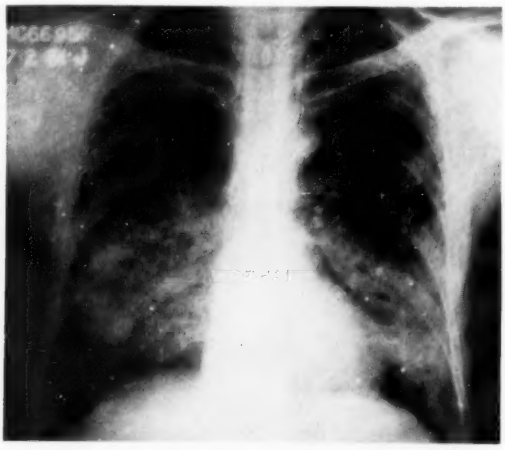

Fig. 5.—Extensive pulmonary involvement is commonly encountered in South American blastomycosis.

case, because of the lack of specificity of the symptoms, the diagnosis is made only at autopsy.[46]

Appendicular lesions have been studied by several authors.‖ Involvement of the anorectal region has been reported.¶

Other Organs: The spleen and liver may be enlarged. Peritoneal localization has been reported.[44] Involvement of many other organs has been observed occasionally, producing highly variable clinical pictures.[41]

DIFFERENTIAL DIAGNOSES

South American blastomycosis is a markedly polymorphic disease and must be differentiated from a large number of clinical entities. Lymphadenopathy being a prominent feature, scrofuloderma and Hodgkin's disease should be primarily con-

‖ References 56, 36, and 45.

¶ References 42 and 43.

sidered, then other deep mycoses such as North American blastomycosis, coccidiodomycosis, actinomycosis, histoplasmosis, cryptococcosis, and sporotrichosis. Leishmaniasis, yaws, syphilis, certain neoplasms, and aleukemic leukemia should be borne in mind. In the cases presenting initial lesions limited to the oral mucosa, certain manifestations of vitamin B complex deficiency, aphthous stomatitis, periadenitis mucosa necrotica recurrens (Sutton), and Vincent's stomatitis should be considered.

IMMUNOLOGY

Cutaneous Test.—The intradermal injection of antigens prepared from cultures or pus has not yielded uniform results in the hands of different investigators.# Almeida, Lacaz, and Cunha,[58] after comparing various antigens, concluded that the best is prepared from filtered cultures of mixtures of numerous samples (they used 19) in liquid Sabouraud's medium, maintained during three months at 22 to 26 C. They consider the intracutaneous test of value both in diagnosis and in prognosis. In the severe forms of the disease the cutaneous reaction is negative, showing a state of anergy. In a limited number of individuals tested by one of us (T. A. F.) using an antigen furnished by Lacaz, the specificity of the test did not appear convincing.

Complement Fixation Reaction.—The standardization of this reaction has not yet been achieved.*

PATHOLOGY

The macroscopic and microscopic changes in the tissues are not specific and are similar to those found in other deep mycoses, more closely resembling those in North American blastomycosis.

Biopsy.—The histopathological changes are those found in a nonspecific granuloma, and diagnosis can be assured only by the finding of the fungus. The granuloma may be of the tuberculoid or of the foreign body type. The epidermis may reveal ulceration, microabscesses and epithelial hyperplasia, sometimes simulating carcinoma. Abscess formation may occur in the reticular corium, in which neutrophiles predominate, but lymphocytes, plasma cells, and a few eosinophiles may also be found. The fungus may appear in the interior of the giant cells, in the abscesses, in the microabscesses, or elsewhere in the corium or in the epidermis.

The finding of a tuberculoid reaction does not indicate that the organism is absent in the lesions as postulated by Jadassohn and Lewandowski's law. In fact, nonspecific acute inflammatory and tuberculoid or foreign body reactions have been demonstrated side by side in the same section,[61] similar to the picture seen in coccidioidomycosis.

Autopsy.—The predilection of the fungus for the lungs is a remarkable fact. Contrary to the work of former investigators, who reported infrequent pulmonary involvement, Fialho † found it in 84% of the 25 patients on whom he performed autopsies. Nodules, cavitary lesions, and abscesses are found. Some nodular lesions may undergo regressive changes and calcification. The lymphatic tissue is usually affected. Gummatous lesions, necrosis, necrobiosis, and fibrosis are common. Lesions

References 13 and 57.

* References 59 and 60.

† References 49 and 63.

are common in the digestive tract, the mouth, the pharynx, and the portion from the jejunum to the anus. In the latter segment, round ulcers formed consequent to previous ulceration in the underlying lymphoid tissue may become confluent and form large ragged ulcerated areas. Involvement of the skeletal system is not as rare as previously believed.

MYCOLOGY

The great majority of investigators agree that one single species of fungus is the agent of South American blastomycosis. However, its taxonomic position is still controversial. Without giving preference to any of the designations suggested, we limit ourselves to listing them all chronologically and shall express our own opinion in a future communication.

Following is the list of designations: Oidium brasiliensis, Splendore, 1912; Blastoporidium schooi, Hartmann, 1912; Zymonema brasiliense, Splendore, 1912;

Fig. 6.—Multiple buds distributed around the periphery of the parent cell resemble, in cross-section, a marine pilot's wheel.

Mycoderma histoporecellure, Brumpt, 1912, (also Nannizzi, 1934, Ciferri and Redaelli, 1936); Zymonema histoporocellularis, Haberfeld, 1919; Mycoderma histoporocellularis, Neveu-Lemaire, 1921; Monilia brasiliensis, Vuillemin, 1922; Mycoderma brasiliense, Brumpt, 1927; Coccidioides brasiliensis (Splendore, 1912) Almeida, 1929; Paracoccidioides brasiliensis (Splendore 1912, Almeida 1930); Paracoccidioides cerebriformis, Moore, 1935; Protomyces faverae, Dodge, 1935; Paracoccidioides tenuis, Moore, 1938; Lutziomyces histoporocellularis (Haberfeld, 1919) Fonseca, 1939; Blastomyces brasiliensis, Conant and Howell, 1941; Aleurisma brasiliensis, Aroeira Neves and Bogliolo, 1950.

MORPHOLOGY OF THE FUNGUS IN TISSUE

Examination should be made of material collected from pus, exudates, or crushed tissue in direct mount or in stained sections of tissue from man or from guinea pig. The fungus appears principally in two different forms: (*a*) It may appear as multi-

ple budding cells, 10 to 60 μ in diameter, with thick walls giving the appearance of a doubly contoured membrane. The buds may occur at a few points only, or over the whole cellular surface, resembling then in cross section a marine pilot's wheel, which is characteristic of the species (Fig. 6). The buds may be as small as 1 to 2 μ in diameter, resembling cocci, or as large as 10 μ in diameter. They are usually round, but they may be ovoid, ellipsoid, bacilliform, or pyriform. (*b*) The fungus may appear as singly budding cells, 6 to 20 μ in diameter, similar to those occurring in Blastomyces dermatitidis. Chains of budding cells may be formed of varying lengths, either branched or not branched.

In sections stained with hematoxylin and eosin, the cytoplasm is colored purple, blue, or red, depending on the vital phase of the organism.[63] The cytoplasm may show small vacuoles, which by proper fixation and staining may be identified as fat. The Hotchkiss-McManus stain as recommended by Kligman and Mescon [84] reveals the characteristic forms of the organism more clearly. Bogliolo,[31] in his extensive series of cases, compared several staining methods and came to the conclusion that the morphology and the mode of reproduction of the fungus could be studied better with ammoniacal silver impregnation (especially by the Perdrau and Gomori methods) and with preparations made by apposition and stained with ferric hematoxylin or Giemsa. Besides the forms just described, he drew attention to some other morphologic aspects which may have importance in the life cycle of the parasite. The multiple budding process seems to be preceded by profound changes in the nuclear substance, probably karyokinetic in nature, a feature absent in the single budding process. Some cells appear flattened, fragmented, or twisted. Cells in crescent form are seen, which are nevertheless able to multiply. Neither in human tissues nor in the tissues of guinea pigs could he demonstrate any of the special types of sporulation such as the "cryptosporulation" described by Ciferri and Redaelli,‡ and the "exogenous sporulation" described by Fonseca Filho.§ He interpreted the minute colorless zones in the wall of the parent cell which were previously considered orifices as unstained spots where the buds or daughter cells are destined to arise. At these spots, the capsule becomes thinner, more elastic and distensible, so that small chromatin masses surrounded by small amounts of protoplasm can easily push outwards to form the small buds. He observed the continuity of the membrane of the parent cell with the membrane of the buds and also the passage of chromatin through the pedicle uniting them. In preparations stained with Giemsa, the thinned-out zones of the membrane where buds are formed are easily visible. The multiple budding process is more often found in lymph glands and in the spleen. In epithelium, especially if ulcerated, and in the internal organs, chiefly the lungs, the multiple budding forms are rare and may even be absent. For this reason, research in this disease should not be confined to histological studies, for if the specific multiple-budding forms are not found, it may be impossible to differentiate between South American and North American blastomycosis. Moore [68] drew attention to the fact that the finding of single budding cells probably explains why some cases reported from South America have been diagnosed as Gilchrist's disease.‖ De Mon-

‡ References 64 and 65.

§ References 66 and 67.

‖ References 69 to 72.

breun [73] reported as another possible explanation the multiple budding which occurs in blood agar cultures of B. dermatitidis at 37 C. This was also observed by Conant and Howell,[74] who found these forms in fresh preparations of material obtained from mice infected with cultures of B. dermatitidis.

CULTURES

Cultures obtained from infected material (pus, exudate, sputum, curettings, or biopsy specimens from cutaneous lesions and lymph nodes) grow very slowly.

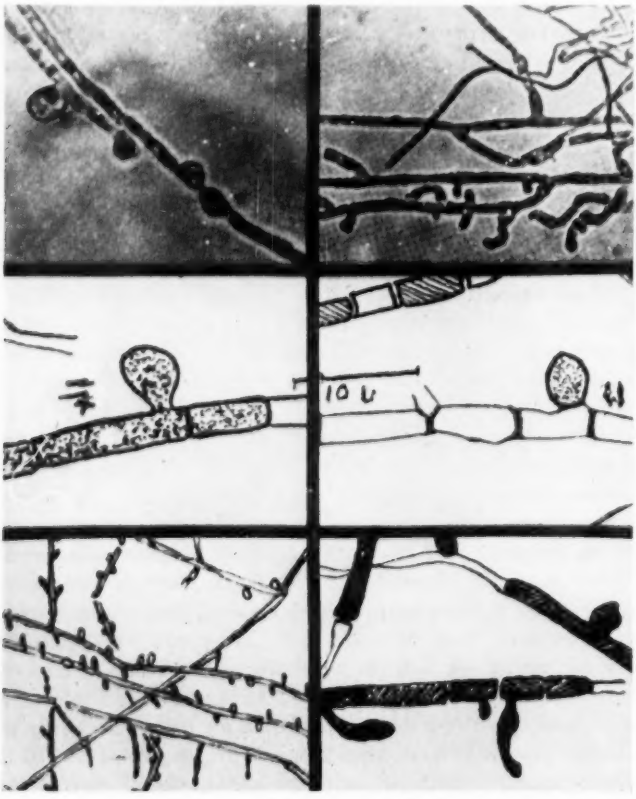

Fig. 7.—Illustrating the characteristic "aleurispores" which led Aroeira Neves and Bogliolo to suggest the name "Aleurisma brasiliensis for this fungus. (Courtesy of Mycopathologia et Mycologia Applicata.[33])

Usually the colony first appears in about 20 days; sometimes not for 90 days. However, subcultures grow more rapidly. Many authors have obtained positive cultures from peripheral blood, confirming the hematogenous manner of dissemination of the disease; the method should not, however, be relied upon as a diagnostic procedure, for the percentage of negativity is high.[41] The selection of the medium to be used is important for the diagnosis.[60] Material aspirated from lymph nodes not yet fistu-

lized should be streaked on enriched media such as blood agar or chocolate agar, adjusted to a pH ranging from 7.2 to 7.6. If the material is likely to be contaminated, it should be cultured on Sabouraud's dextrose agar, which has a pH lower than 7, to inhibit the growth of bacteria.

The gross appearance of the colony depends on the medium and on the temperature. The optimum temperature ranges from 25 C. to 30 C. In plain agar with pH 7.4, the colonies are white to yellowish and cerebriform. In media containing carbohydrates and lower pH (Sabouraud's), the colonies are white, wrinkled, and firm, and present aerial mycelia. With age, the colonies may turn brown and the agar splits. At 37 C., the fungus develops only smooth to cerebriform, yeast-like colonies.

Microscopic examination of cultures grown at room temperature reveals branched and septate mycelia with intercalary or terminal chlamydospores.[27] In slide cultures, it is easy to follow the formation of mycelia. In old cultures and in cultures grown at 37 C., single and multiple budding, yeast-like cells identical with the tissue forms, may be observed.

Mycologic study of the parasite should be completed by other methods. In liquid media the colonies are formed in the bottom of the tube and may adhere to its sides at small distances upward.[27] Some growth may be obtained under anaerobic conditions. There is little or no enzymatic action on sugars; little or no growth occurs in potato medium and no reduction of nitrates to nitrites.[41]

Recently, Aroeira Neves and Bogliolo[33] reported the results of their studies of several strains of the fungus on various artificial media. Cornmeal agar proved the most suitable medium, stimulating the production of spores and inhibiting the formation of nondifferentiated cottony mycelium and yielding constant macroscopic and microscopic findings sufficient for a satisfactory taxonomic study of the fungus. The microscopic examination of fully developed adult colonies (40 days old) reveals the characteristic "aleurias" or aleurospores (Fig. 7). They differ from true conidia because they do not separate immediately from the mycelium by natural processes of dehiscence but remain attached to the dead and empty hyphae. The aleurospores appear laterally with or without a pedicle. They may be pyriform, flattened, quadrangular, or with one of their sides curved. Aroeira Neves and Bogliolo[33] found them in all cultures examined; indeed they have been consistently observed by the former since 1922.

ANIMAL INOCULATION

Many authors ¶ have studied South American blastomycosis in experimental animals. Intratesticular inoculation into guinea pigs serves best. After a few weeks, an orchiepididymitis develops, usually remaining localized. Exceptionally, lesions may be found in the regional lymph nodes and in the spleen. Microscopic examination shows the characteristic tissue form of the organism, already described.

Successful intraperitoneal inoculation in mice, with saline suspensions of pure cultures of the yeast-like phase from cultures grown at 37 C., was reported by Conant and Howell,[74] after limited experiences in seven animals. Generally the lesions produced tended toward involution rather than progression. Nodules, rich in parasites, were found in the mesentery, liver, spleen, and diaphragm.

¶ References 19 and 76 to 79.

PROGNOSIS AND TREATMENT

Before the introduction of the sulfonamides, the disease was usually fatal, but recently the prognosis has changed. Life expectancy has been highly improved and clinical cures have even been reported.

In the past, many drugs were tried without success, including iodides, gold compounds, dyes (methylene blue, methylrosaniline chloride, acriflavine), and antimony salts. Electrocoagulation of localized lesions was claimed to be of value. Almeida [27] reported good results with "specific" vaccines.

In 1940, Oliveira Ribeiro [80] used sulfapyridine with success in a group of patients. Since his first report, several sulfonamides have been tried and benefit has been claimed. In vitro experiments by Pellegrino [82] revealed the activity of the various compounds in decreasing order to be as follows: sulfadiazine, sulfapyridine, sulfanilamide, sulfacetimide (Albucid), Soluseptazine, Anaseptyl, sulfathiazole and Prontosil soluble. No clinical data are as yet available to show if there is any parallel action in vivo. Sulfadiazine is the preparation most extensively used in practice, in the total dosage of 2 to 4 gm. a day, fractionally administered. Clinical improvement can be expected in the great majority of patients, but "clinical cure" has been achieved only in a smaller number. Relapses are frequent when the drug is discontinued. The toxicity of the "sulfa" compounds during the long continued administration required in such a chronic disease is a great disadvantage. It is the belief of one of us (T. A. F.[83]) on the basis of his own limited experience that there has been too much enthusiasm in the evaluation of sulfatherapy in this mycosis.

SUMMARY AND CONCLUSIONS

From all languages the literature which pertains to the subject of South American blastomycosis has been reviewed. Considerable change in the concept of the pathogenesis of this disease has occurred in recent years. In this communication, the important facts are furnished in English.

The disease exhibits a marked predilection to involve primarily the gastrointestinal tract; the oral and nasopharyngeal cavities must be included in the term.

Contrary to previous belief, pulmonary involvement is commonly encountered, probably as an extension from the pharynx.

Lymphoglandular, cutaneous, and generalized involvement occur frequently, but probably only secondarily to the other types.

The name most recently advocated in South America for the causative organism is Aleurysma brasiliensis.

Prof. L. Bogliolo, Belo Horizonte, Brazil, and Prof. C. S. Lacaz, São Paulo, Brazil, furnished part of the material used in this paper.

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LUPUS ERYTHEMATOSUS

Treatment by Combined Use of Massive Amounts of Panthothenic Acid and Vitamin E

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CINCINNATI

THIS REPORT deals with rationalization for the use of, and results obtained in the treatment of, certain phases of lupus erythematosus by the administration of massive amounts of pantothenic acid (calcium and sodium salts, and the alcohol thereof) and vitamin E. Patients who had chronic discoid, disseminated discoid, and subacute disseminated lupus erythematosus were studied. Maintenance therapy of patients with acute disseminated lupus erythematosus controlled by steroid hormones was likewise studied. Results were reported on the basis of preliminary study in 1951.[1] Confirmation of these results after further study and additional data follow.

THERAPEUTIC AGENTS EMPLOYED

Pantothenic Acid

Pantothenyl alcohol (Panthenol) *	consisting of the alcohol of pantothenic acid, which is, chemically, *d*-α, γ-dihydroxy-N (3-hydroxypropyl) β, β-dimethylbutyramide.
Calcium pantothenate, dextrorotatory †	consisting of the calcium salt of pantothenic acid, the molecule of which is composed of β, β-dimethyl-α-hydroxybutyroactone condensed with β-alanine.
Calcium pantothenate, racemic ‡	consisting of the calcium salts composed of an equal number of dextro- and levo-rotatory constituents.
Sodium pantothenate, dextrorotatory §	consisting of the sodium salt of pantothenic acid.

Vitamin E

The following forms of vitamin E were used in this study:

Ephynal acetate ‖	consisting of *dl*-α-tocopherol acetate (synthetic vitamin E acetate).

Read at the meeting of the American Dermatological Association, Lake Placid, N. Y., June 11, 1953.

* Panthenol for study was supplied by Hoffman-LaRoche, Inc.

† Calcium pantothenate, dextrorotatory, for this study was supplied by Lederle Laboratories Division, American Cyanamid Company; Merck & Company, Inc.; National Oil Products Company; Chas. Pfizer & Company, Inc.

‡ Calcium pantothenate, racemic, for this study was supplied by Abbott Laboratories.

§ Sodium pantothenate, dextrorotatory, for this study was supplied by Parke, Davis & Company.

‖ Ephynal acetate for this study was supplied by Hoffmann-LaRoche, Inc.

Natopherol acetate ¶	consisting of vitamin E concentrates containing *d*-α-tocopherol acetate with related tocopherol acetates. Each 100 mg. contains 73 mg. of *d*-α-tocopherol acetate, equivalent to 100 mg. of *dl*-α-tocopherol, by rat antisterility assay comparing the activities of *d*-α-tocopherol and *dl*-α-tocopherol; or equivalent to *d*-α-tocopherol 108 mg. by rat antisterility assay, comparing the activities of *d*-α-tocopherol and *d*-α-tocopheryl acetate.
Aquasol E #	consisting of a water-soluble form of *d*-α-tocopheryl acetate, equivalent in vitamin E biological activity to 100 mg. of *dl*-α-tocopherol (oil-soluble vitamin E made water-soluble with sorethytan esters).

RATIONALIZATION FOR THE USE OF PANTOTHENIC ACID COMBINED WITH VITAMIN E

Pantothenic Acid

Much research has been done (and continues) to establish the role of pantothenate as a vitamin and the metabolic functions of pantothenic acid.[2] Symptoms of nutritional deficiency of pantothenate reveal "only the lack of a substance fundamental to cellular physiology in general could cause such diverse symptoms."[3]

It is fairly well established, now, that as nutritional deficiency of pantothenate progresses, certain vital metabolic processes slow down and cease. This will result in incomplete synthesis of functional enzymes and coenzymes, which will have the effect of causing deficiencies of other factors.

Some of the more important manifestations of pantothenate deficiencies are the following:

1. Lesions of the skin and hair.*
2. The storage of riboflavin.[9]
3. Gastrointestinal symptoms.†
4. Lesions of the nervous system ‡
5. Inhibition of antibody formation (pantothenate and pyridoxine deficiency leads to severe impairment of antibody production) §
6. Lesions of the adrenal gland

Observations seem to demonstrate that in pantothenate deficiency the adrenal cortex is depleted of hormone, although there are opposing views explaining the cause of this adrenal change. One of these views suggests that adrenal changes reflect functional insufficiency of the gland due to inability to synthesize hormone, implying that in some manner, pantothenate is directly concerned with hormone synthesis.‖

Evidence suggests functional inadequacy of the adrenal cortex during pantothenate deficiency.[21] Pantothenate-deficient animals have a lowered fasting blood

¶ Natopherol Acetate for this study was supplied by Abbott Laboratories, and Distillation Products Industries, Division of Eastman Kodak Company, kindness of Dr. Norris Embree.

Aquasol E was supplied by U. S. Vitamin Corporation.

* References 4 to 8.

† References 10 to 12.

‡ References 13 and 2.

§ References 14 and 16.

‖ References 17 to 20.

sugar and increased sensitivity to insulin, both observations being consistent with adrenal insufficiency. In the vitamin-deficient state, deficient animals are unable to respond to epinephrine or corticotropin (ACTH) by lowering eosinophiles.¶

The injection of cortisone causes the deficient animals to behave like normal animals in eosinophile response. The fact that deficient animals respond like normal animals to cortisone is taken to indicate that the mechanism of response is intact but the animals are unable to elaborate the hormone.

Changes which the adrenal gland undergoes during pantothenate deficiency show that pantothenate is involved in the synthesis of adrenal cortex hormones. In pantothenic acid deficiency there develops a definite insufficiency of adrenocortical function.[24]

According to Cowgill: "Pantothenic acid is needed in the chemical process by which the adrenal gland produces certain of its hormones, and may be considered a biological catalyst."#

In 1950, Maas and his co-workers[27] showed that Escherichia coli actually excretes pantothenate.

It is recognized that pantothenate exists in tissues in bound form. In 1945, discovery was made of a coenzyme, coenzyme A (CoA),* of which pantothenate is a constituent. It appears that pantothenic acid, probably acting through coenzyme A, is necessary for the biosynthesis of the adrenal steroids.[24]

Nutritional deficiency of pantothenic acid leading to greatly reduced coenzyme A levels in tissues would adversely affect many other reactions. Synthesis of acetylcholine would be deranged; likewise, the acetylation of glucosamine and galactosamine would be reduced.[2] Since these compounds are components of connective tissue, there may result abnormalities of this type of tissue.

It has been emphasized that lesions of the chronic discoid and acute types of lupus erythematosus are pathologically alike, and, as Klemperer has so ably pointed out, the common denominator is the connective tissue.[30]

Continuing and advancing research for knowledge about pantothenate and enzymatic steps in its conversion are indicated by announcement of the synthesis of pantothine, reported at the most recent meeting of the American Chemical Society.[31]

It is concluded from the foregoing that in pantothenic acid deficiency there is an insufficiency of adrenocortical function.

Vitamin E

The term "vitamin E" has been applied to α-tocopherol, and, to a less extent, to the β, γ, and δ tocopherols, and certain synthetic compounds.

The deficiency state experimentally (or accidentally) induced in laboratory and domesticated animals is characterized by manifestations varying from encephalomalacia and exudative diathesis in the chick, to fetal absorption, testicular damage, muscular dystrophy, and other effects in mammals.†

¶ References 22 and 23.
# References 25 and 26.
* References 28 and 29.
† References 32 to 40.

The serum tocopherol levels in normal adults and in those suffering from disease have been extensively studied.‡ Such studies indicate that the mean serum level of tocopherol is less than normal in malnourished persons, as well as in persons with disease states, particularly those associated with impaired absorption of fats.§

The tocopherols, likewise, possess the power to augment other vitamins. Individuality of vitamin E, the modifying agent, may not be evidenced, but it undoubtedly influences the physiological activity of other vitamins. This phenomenon has been described as "sparing" or "synergistic" and has lead to application of the term "covitamin E" activity.‖

The tocopherols are phenolic antioxidants. In general, any acid-type inhibitor will promote or energize the activity of any phenolic antioxidant. Ascorbic acid (vitamin C) enhances the antioxygenic activity of the tocopherols.[57] In addition, vitamin C, because of its marked reducing activity, protects vitamin E in the intestinal tract.[58]

Vitamin E protects biotin and other members of the vitamin B complex against destruction by rancid fats in the intestinal tract.[59] Vitamin E also protects against phosphorus turnover.[60]

SUMMARY OF INVESTIGATIVE STUDIES

Vitamin E and Pantothenic Acid Derivatives Used Individually in the Treatment of Lupus Erythematosus

Klemperer's study of the pathology of disseminated lupus erythematosus in relation to involvement of various organs described skin changes[61] as homogenization of collagen fibrillae and ground substance, with concomitant proliferation of fibroblasts and degenerative "stigmas," which seemed to indicate involvement of connective tissue. Vascular changes in the skin and elsewhere follow a pattern of connective tissue involvement.

Vitamin E.—Burgess,¶ observing that tocopherols in sufficient dosage demonstrated ability to regenerate collagenous tissue in a case of noduloulcerative granuloma with lipoidal deposits indistinguishable from necrobiosis lipoidica diabeticorum, and, reasoning that lupus erythematosus affected primarily collagenous ground substance, studied mixed tocopherol therapy in the treatment of lupus erythematosus. He reported favorable results after prolonged therapy followed by maintenance therapy after clinical cure.

Sweet[64] failed in attempted confirmation of Burgess' results on tocopherol therapy. Sawicky[65] likewise reported failure. Morgan[66] agreed with Sweet. A group of investigators at New York University Hospital[67] studied tocopherol therapy for discoid lupus erythematosus and other dermatoses, using both oral and injectable materials, and confirmed Morgan's results.

Study of the effectiveness of tocopherols (in keeping with the ideas of Burgess and Pritchard) during a period of 14 months was undertaken on 60 cases of localized and disseminated discoid types. "Real and effective" action was reported on 15 patients. The large proportion of failures was attributed to insufficiency of the

‡ References 41 and 42.
§ References 43 to 48.
‖ References 49 to 56.
¶ References 62 and 63.

dosages utilized.[68] Vitamin E administered orally, daily, produced definite amelioration but not absolute cure of chronic lupus erythematosus.[69] Vitamin E induced complete cure of poikiloderma and lupus erythematosus; the latter recurred and was again "cured" with tocopherol therapy.[70]

Of a series of 25 patients with lupus erythematosus treated by oral administration of vitamin E, 17 recovered but 2 relapsed within six months after cessation of treatment. Four patients showed improvement: four became worse.[71] Successful management with vitamin E was reported in 10 cases of chronic lupus erythematosus which had previously responded to other therapy and then relapsed.[72] Several cases of lupus erythematosus were treated with vitamin E with beneficial results. Erythema and infiltration diminished in a few weeks and cleared completely after a few months with tocopherol therapy.[73]

Pantothenic Acid.—Goldman [74] reported results of treatment of subacute discoid lupus erythematosus with calcium pantothenate. He concluded that calcium pantothenate offered possibilities as the least toxic of available chemotherapeutic agents for prolonged therapy. He followed his first report with a favorable preliminary study on intensive pantothenyl alcohol therapy.# Cochrane and Leslie [77] failed in attempted confirmation of Goldman's results.

ANALYSIS OF CLINICAL DATA

Sixty-seven patients who had lupus erythematosus (diagnosis confirmed by biopsy) were treated with massive-dose therapy consisting of pantothenic acid derivatives combined with vitamin E. Patients are classified according to the disease phase presented.

No. of Patients	Disease Phase
36	Chronic discoid
17	Disseminated discoid
11	Subacute disseminated
3	Acute disseminated

Twenty-eight of this group had had no previous therapy. Thirty-nine had had previous treatment, consisting of prolonged and diversified types of therapy including gold, bismuth, arsenic compounds, liver, salicylates, and steroid hormones. All of these patients improved.

Chronic Discoid Group.—This group was comprised of 36 patients.

No. of Patients	Cleared to Date, %
15	100
6	95
6	90
3	80
3	75
3	60-70 *

* Therapy started too recently for adequate appraisal of response.

Patients in this group had had the disease for time intervals of 10 to 30 years. Considerable amounts of scarring were observed, on original examination, among those patients who had had previous therapy with solid carbon dioxide, x-ray,

References 75 and 76.

radium, or acid. Most of the lesions presented were markedly infiltrated and hypertrophic. Nine patients had experienced episodes of the disseminated discoid phase of the disease.

Objective improvement in the average patient, in this group, began after (approximately) four months, after (approximately) six months for those patients with lesions of many years' duration and marked hypertrophy.

Arthralgia developed in 10 patients while under treatment. Response to the addition of sodium salicylate in eight of these patients was prompt. In the other two patients, response occurred after removal of dental foci.

Eighteen additional patients with chronic discoid lupus erythematosus began treatment with massive-dose therapy consisting of pantothenic acid derivatives combined with vitamin E. Most of them showed some improvement, but all of them disappeared from observation after one or two months.

Disseminated Discoid Group.—This group was comprised of 17 patients.

No. of Patients	Cleared to Date, %
7	100
4	95
2	90
4	80 †

† Therapy started too recently for adequate appraisal of response.

Objective improvement was noted after (approximately) two months.

Subacute Disseminated Group.—This group was comprised of 11 patients.

No. of Patients	Cleared to Date, %
9	100
2	75 †

† Therapy started too recently for adequate appraisal of response.

Response to therapy was most rapid, and best, among these patients, and was manifested (usually) in one month.

Acute Disseminated Group.—This group was comprised of three patients. These patients were started on massive-dose therapy of the agents under study while the acute phase of the disease was being brought under control with steroid hormones. These patients have been maintained on massive-dose therapy without relapse, for time intervals as follows: 7 months, 11 months, and 19 months, respectively.

In general, the more hypertrophic and infiltrated the process, the slower the response. It has been necessary to persist with therapy for as long as three years in some patients.

In some patients therapy was not continuous but was interrupted for various reasons. In those patients, progress ceased, and if therapy stopped for long, relapse occurred, or new lesions developed. Eleven patients developed new lesions while undergoing therapy, but such lesions were short-lived and usually faded out before existing older lesions were completely controlled. It was possible to maintain maximum dosage schedule, for some patients, only during the last four months of treatment course.

In all patients not yet completely cleared, improvement has been marked. Patients not cleared entirely are still under treatment.

After clearing, the lesions exhibited minimal residual atrophy and pigment disturbance. Even the old scars of previously treated, inactive lesions flattened,

smoothed out, and lost most of the telangiectasia. These changes in old scars may have resulted from the action of prolonged use of vitamin E on the collagen and fibrous tissues in the lesions and blood vessels.

Patients who had maintained the massive-dose therapy program for some months regularly volunteered the information that they "felt better," or that they "had a sense of well-being." This feeling had no relation to objective change in the skin lesions. This reaction simulated the euphoria experienced by some patients taking cortisone.

TREATMENT PROGRAM

Early in this study, patients were treated with combined use of relatively small amounts of one of the pantothenic acid derivatives and one of the vitamin E preparations. Later, when it became apparent that higher dosages were required, the following schedule was employed:

Pantothenic acid	
Calcium pantothenate	10-15 gm. daily
Pantothenyl alcohol	10-15 gm. daily
Sodium pantothenate	5-10 gm. daily
(The nature of this light crystalline substance permitted inclusion of only 0.25 gm. per capsule. Difficulty presented by daily number of required capsules necessitated use of smaller amounts of this agent.)	
Vitamin E	
Ephynal acetate	1,000-2,000 mg. daily
Natopherol	1,000-2,000 mg. daily
Aquasol E	1,000-2,000 mg. daily

COMPLICATIONS ARISING FROM THERAPY

As has been previously reported,[1] there were no complications arising from this treatment program except for transient nausea and gastric distress. It was previously reported that such distress occurred chiefly with pantothenyl alcohol, but as the present study progressed, it was found that transient nausea and gastric distress occurred about equally from use of calcium pantothenate, sodium pantothenate and pantothenyl alcohol. Symptoms of such distress occurred in only a few patients, and no patient was found who could not take one of the pantothenic acid derivatives studied.

No abnormalities were revealed by repeated hematological studies and urinalyses of patients kept on this program of therapy for intervals varying from one to three years.

Varying combinations and massive dosages of pantothenic acid derivatives and vitamin E preparations were given to 154 patients who had diseases other than lupus erythematosus. There was no complication, except for gastric distress abovementioned.

LABORATORY DATA

Urinary Excretion Levels—Pantothenic Acid Derivatives‡ (Morning Urine Specimens)

Average level before start of therapy in patients with lupus erythematosus was 24.24 γ/ml. Five patients had levels averaging somewhat higher than the others. It was noted, however, that these patients had been taking large quantities of multiple-vitamin preparations containing pantothenic acid, vitamins A, C, E, and components of the vitamin B complex, including riboflavin, inositol and pyridoxine.

‡ These studies were done by Hill Top Research Institute, Inc., Cincinnati.

Average level of normal persons used as controls was 2.69 γ/ml.

Average levels of patients under treatment were as follows:

Oral Daily Dosage, Gm.	Calcium Pantothenate γ/Ml.	Pantothenyl Alcohol (Panthenol) γ/Ml.
5	1,865.2	3,891.1
7½	3,624.3	5,036.4
10	4,034.8	5,732.7
12½	8,496.8	13,144.1
15	15,750.0	17,945.0

Levels higher than those for calcium pantothenate, but not so high as those for pantothenyl alcohol at the same dosages, were obtained from patients on sodium pantothenate. Because of the bulk of this material, however, the agent was impractical for use in this study.

The increase in excretion of pantothenic acid (over that of normal persons) in patients with lupus erythematosus before start of therapy may be indicative of some metabolic fault in patients with lupus erythematosus.

The increased urinary excretion levels of pantothenic acid exhibited with increase in dosage levels of pantothenic acid derivatives justifies the dosages employed and may account for the more rapid clinical improvement on the higher dosages.

For this study, the method of Hoag, modified to include use of pantothenate assay medium, dehydrated Difco No. B-323 as the test medium, was employed.§

In order to obtain greater accuracy, determinations of pantothenic acid blood levels instead of urinary excretion levels have recently been undertaken. The findings parallel closely the urinary excretion levels, but show less variation.

Vitamin E Blood Levels ‖

Average level before start of therapy in patients with lupus erythematosus was 0.567 γ/100 ml. serum

Six patients had levels averaging 2.060 γ/100 ml. serum but it should be noted that these patients had been taking large quantities of multiple-vitamin preparations containing vitamins A, C, E, and components of the vitamin B complex, including folic acid, inositol, and B_{12}. High vitamin E levels may have been due to ingestion of vitamin C, because of the latter's reducing action which protects vitamin E.

Average level of normal persons used as controls was 2.370 γ/100 ml. serum.

Average levels of patients under treatment were as follows:

Oral Daily Vitamin E-All Types, Dosage, Mg.	Average Blood Level γ/100 Ml.
500	2.59
1,000	4.38
1,500	5.58
2,000	6.49

Effort was made to determine the average blood levels (expressed as mg./100 ml. serum) produced by each of the oral vitamin E preparations available for this study.

Dosage, Mg.	Ephynal	Natopherol	Aquasol E
500	2.54	2.66	3.11
1,000	2.80	4.48	5.27
1,500	5.46	5.17	6.30
2,000	5.67	5.87	7.12

Vitamin E preparations for parenteral administration were given weekly, because it was impossible to get patients in for treatment oftener than at weekly intervals. All parenterally administered preparations produced significant rises in vitamin E blood levels. Supplementation

§ References 78 and 79.

‖ Early studies were done by Dr. L. J. Filer Jr., Rochester, N. Y. Later studies were done by Hill Top Research Institute, Inc., Cincinnati.

of oral administration, with parenteral administration, appeared to speed up response in recalcitrant patients on oral massive-dose therapy of vitamin E, combined with one of the pantothenic acid derivatives. Additional studies are being undertaken with materials for parenteral administration.

Patients with lupus erythematosus were shown, by laboratory data, to have vitamin E blood levels lower than normal. The increase in blood levels with the increase in dosage of vitamin E, justifies use of massive-dose therapy, and may explain the more rapid rate of favorable clinical response obtained at the higher dosage levels.

For this study, the micromethod of Quaife was modified so that ordinary 10 mm. cuvettes might be employed.[80]

Carotene Levels ¶

Average level before start of therapy in patients with lupus erythematosus was 75.6 γ/100 ml. serum. (This is lower than the reported normal levels of 169.0 [81] and 166.0 for men, and 187.0 for women.)[82]

Average level for normal persons (in our laboratory) was 142.4 γ/100 ml. serum.

Levels rose, with vitamin E levels, in patients with lupus erythematosus under treatment with massive-dose therapy of Vitamin E combined with one of the pantothenic acid derivatives.

COMMENT

The foregoing clinical data represent the investigator's second report on a series of patients with various phases of lupus erythematosus treated with massive doses of pantothenic acid derivatives and vitamin E. Results of a preliminary study have already been reported.[1]

The work of other investigators using these therapeutic agents individually, rather than in combinations, has been summarized. Results from their studies, for the most part, were unfavorable.

The following postulation is offered to explain why use of either of the individual agents, alone, is a therapeutic failure, and why use of the combined agents produces favorable response.

1. Pantothenic acid, a B vitamin, is needed in the chemical process by which the adrenal gland produces certain of its hormones.

2. All four known tocopherols (*α*, *β*, *γ*, *δ*) contain a phenolic hydroxyl group, the structural function of which is the potential oxidizability to a *p*-quinonoid form (which is important for antioxidant power).

3. *α*-Tocopherol may not form a reversible oxidation-reduction system with the *p*-quinone, but there may be intermediate oxidation products, perhaps semiquinones, which could be in equilibrium with tocopherol to furnish the oxidation-reduction mechanism for antioxidant action.

4. If *α*-tocopherol is oxidized, the *p*-quinone can be produced. The *p*-quinone may give an equilibrium with tocopherylhydroquinone, a trihydroxy compound.

5. Tocoherol and tocopherylquinone have already been identified on the basis of their distribution constants and absorption spectra in extracts of stools collected during control periods and during periods when tocopherol was orally administered, supporting the hypothesis that tocopherol is oxidized to its quinone in the body. Other reducing materials including the carotenes were shown to be present in feces.#

¶ These studies were done by Hill Top Research Institute, Inc., Cincinnati.

References 83 and 84.

6. By oxidation at different points of the cyclopentenophenanthrene nucleus there may be obtained probable precursors of cholic acid, of adrenal cortex hormone and progesterone, and of estrogenic and androgenic hormones.

A sufficient supply of vitamin E should act on the anterior pituitary gland to produce a cholesterol-degrading hormone capable of promoting these oxidations. Such a hormone is reported to have been obtained from the anterior pituitary glands of pregnant guinea pigs previously treated with vitamin E.[85]

7. Under the influence of vitamin E, the production of the hormone in the anterior pituitary gland is stimulated and its action is promoted so that normal dehydrogenation of cholesterol is encouraged in the human body and its abnormal dehydrogenation to carcinogenic compounds is prevented.[85]

8. Furthermore, by means of the Thorn test (decrease of eosinophiles in blood) and of the formalin test (counteraction of the inflammation produced by intracutaneous injection of formalin) vitamin E has been found to have activity similar to adrenocorticotropic hormone and to cortisone.[86]

The precise interrelationship of the adrenals, the pituitary, and the various tissues of the body is not clearly defined. Moreover, the functions and modes of interplay of the individual steroid hormones produced by the adrenal cortex are extremely complex.

The present concept is that the action of cortisone and other cortical steroid hormones is entirely mediated through stimulation of the adrenal cortex by the adrenocorticotropic hormone. This hormone is elaborated by the anterior pituitary. The function of the anterior pituitary is, presumably, controlled to some degree by the hypothalamus, which, in turn, can be influenced by higher brain centers.

The adrenocorticotropic hormone has the specific function of regulating activity of the adrenal cortex. It is in response to the action of this hormone that the adrenal cortex secretes its steroid hormone.

It is suggested that the metabolic products of vitamin E, such as the quinones, may serve as "building blocks" to aid in the formation of cortisone-like materials, which are presumed to be excreted by the adrenals. Calcium pantothenate may be an additional biological catalyst, along with the adrenocorticotropic hormone to help aid in the formation of new cortisone-like materials. It is necessary to use extremely large quantities of calcium pantothenate as a catalyst because most of it is quickly metabolized in the body.

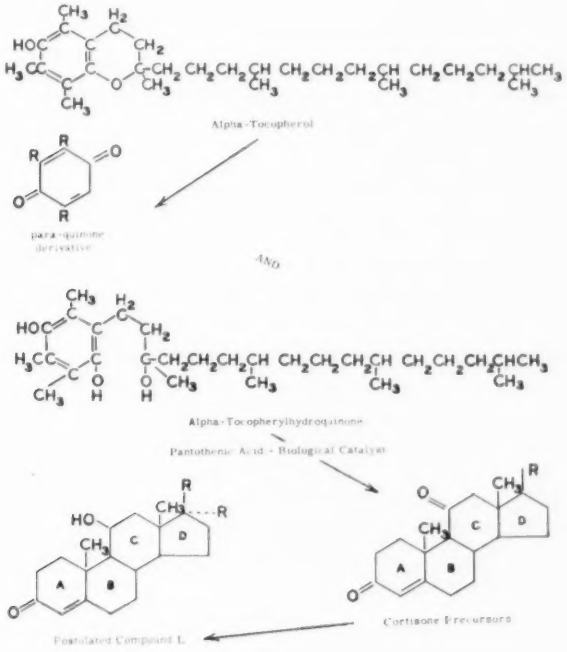
Furthermore, it may be that the combined catlytic activity of the adrenocorticotropic hormone and calcium pantothenate on vitamin E metabolites may produce within the body even more potent cortisone-like bodies than cortisone itself, since it is now known that compounds, such as, 9-α-chloro-17-α-hydroxycortisone have been found to have three to four times the activity of that of cortisone.[87]

During the past few years, much valuable and intensive work has been directed toward clarifying the fundamental mechanism of the action of cortisone against disease. It seems likely that the therapeutic action of cortisone involves not only the many known physiological properties of the hormone but various thus far undis-

covered effects on the chemical processes, organs, tissues, and cells of both normal and diseased persons. In any event, it has not yet been demonstrated that the mode of action of cortisone can be attributed to a single circumscribed mechanism.

It is postulated that cortisone, or some cortisone-like material is perhaps being slowly synthesized within the body from massive-dose therapy of pantothenic acid derivatives combined with vitamin E. What this material is—is not known. For the sake of convenience, and, pending acquisition of additional knowledge, based on further study, this material is designated as "compound L."

Theories, Postulations, and Theoretical Formulations.—The concept relating to results obtained in the treatment of lupus erythematosus by massive-dose therapy



of pantothenic acid derivatives combined with vitamin E is based on the possibility that vitamin E may be metabolized in the body to *p*-quinones and tocopherylhydroquinones, which may aid in the formation of, or furnish the "building blocks" for some precursor cortisone-like materials; additionally, that calcium pantothenate may be intimately related to the function of secretion and formation of steroid hormones known to be products of the adrenal cortex. This theory is supported by the functional inadequacy of the adrenal cortex during calcium pantothenate deficiency.

It is possible that a deficiency of pantothenate in the body can retard production of cortisone and other adrenal hormones. Pantothenic acid, a B vitamin, may be considered a biological catalyst, and, probably acting through coenzyme A, may be

necessary in the chemical synthesis of steroid hormones secreted by the adrenals. It is possible that pantothenic acid, as well as the adrenocorticotropic hormone, aids in the stimulation of the adrenal cortex and the pituitary in the chemical process of production of cortisone or related derivatives.

Vitamin E in the body may be metabolized to α-tocopherylhydroquinone and α-tocopherylquinone, both compounds found (on rabbits) to be more active when injected intravenously than when given by mouth.[88]

Tocopherylquinones and hydroquinones in turn may be metabolized or further modified to some precursor cortisone-like materials. Quinone might be considered a basic starting material for the biologic synthesis of cortisone, and help build up to the skeleton containing the A, B, C, and D ring structure.

Diagrammatically, this theory is shown in the accompanying chart.

SUMMARY

A program of therapy, comprising combined use of massive amounts of pantothenic acid derivatives and vitamin E, was employed in the treatment of 67 patients with various phases of lupus erythematosus. Response was most favorable. Reactions to therapy were insignificant.

Rationalization for use of program of therapy is outlined.

Summary is recorded of investigative work, by others, employing pantothenic acid derivatives and vitamin E, individually, rather than in combination, for the treatment of various phases of lupus erythematosus.

Laboratory data is presented in support of massive-amounts dosage schedules.

A theory is postulated to account for favorable action of combined use of pantothenic acid derivatives and vitamin E in the treatment of lupus erythematosus.

CONCLUSIONS

Combined use of massive amounts of pantothenic acid derivatives and vitamin E constitutes a safe and effective approach to treatment of patients with chronic discoid, disseminated discoid, and subacute disseminated lupus erythematosus. Limited experience suggests this procedure as maintenance therapy for patients with acute disseminated lupus erythematosus, the acute phase having been controlled through use of steroid hormones.

ABSTRACT OF DISCUSSION

Dr. Clinton W. Lane, St. Louis: Dr. Welsh is to be congratulated for a thorough painstaking study of the chemical reactions of pantothenic acid and vitamin E and a complete review of the various theories concerning their modes of activity in the body. He has stated the reasons why he believes they should be effective in the treatment of lupus erythematosus and has produced statistics to show that the therapeutic results prove his opinions to be correct.

Since the cause of lupus erythematosus is unknown, treatment has for the most part been on an empiric basis. However, two therapeutic ideas have prevailed, the one to administer drugs with an anti-infection property, such as gold, bismuth, arsenic, the salicylates, quinacrine (Atabrine; Mepacrine), and chloroquine (Aralen), the other an attempt to improve the defense mechanism and to boost the resisting powers of the body by the use of liver injections, transfusions, vitamins, adrenocorticotropic hormone and cortisone (Cortone).

Important reasons why Dr. Welsh has chosen to give pantothenic acid are that with a deficiency of this vitamin there is an insufficiency of adrenal cortex hormone and that pantothenate is involved in the synthesis of antibodies. Vitamin E was chosen because it has the power to augment other vitamins and because Welsh agrees with Burgess that tocopherols have the

ability to regenerate collagenous tissue. These appear to be logical and valid reasons, particularly if one agrees that lupus erythematosus pathologically shows primarily a connective tissue involvement. The therapeutic results obtained in chronic and disseminated discoid and subacute disseminated lupus erythematosus are exceptionally good, even though they are much slower and less dramatic than those obtained with quinacrine, cortisone, and gold. The vitamins employed have the added advantage of being nontoxic, even in the high dosages administered for months and years.

The failure of others to obtain the satisfactory results of Welsh, Goldman, and Burgess are traced by these investigators to inadequate dosage, yet several months after Goldman's good results were published, Cochrane and Leslie, using the same dosage of calcium pantothenate and panthenol had 100% failure in 46 patients. Others, and I myself, had similar poor results, and failures were recorded by numerous investigators who attempted to duplicate the fine results obtained by Burgess with vitamin E. It may be that the dosages were inadequate, that not enough time and patience were exercised, and that the proper combination of the two vitamins was not employed.

Dr. Welsh has given vitamin E to patients with lupus erythematosus because the blood level is lower than in normal persons and then gives pantothenic acid because the urinary excretion of pantothenic acid is higher in lupus erythematosus patients than in normal persons. Has he in his additional studies found the blood level of pantothenic acid to be lower than normal and the urinary excretions of vitamin E to be higher than that of normal persons?

The cost of these vitamins in the dosages recommended should be borne in mind. The materials were donated to Dr. Welsh for investigative purposes, but if the patient had to purchase the vitamins in St. Louis in the dosage recommended, the daily cost would vary between $3.00 and $4.50. If this was continued for three years as was necessary in some patients, the total cost of the drugs alone would be almost $5,000. This is a tidy sum even in this golden age when there is little quibbling about the cost of commodities whether desired or necessary.

A correct appraisal seems to be that in these two vitamins we have a safe approach to the therapy for lupus erythematosus and that they should be tried when quinacrine, chloroquine, and more rapidly acting drugs have failed or when toxicity to these drugs has developed. We are indebted to Dr. Welsh for offering us an effective method of therapy in the treatment of a stubborn, chronic dermatosis.

DR. J. H. SWARTZ, Boston: I have had the opportunity of discussing Dr. Welsh's original paper. My associate, Dr. Glicklich and I have used calcium pantothenate in lupus erythematosus in these various dosages mentioned, since Dr. Goldman's paper.

First, a word about the maintenance dose. I have one case in particular that I want to cite, a case of acute disseminated lupus erythematosus, before the cortisone therapy era, who, at least coincidental with the administration of large doses of calcium pantothenate, recovered. Of course, we don't know whether the calcium pantothenate was responsible for the remission except that she relapsed each time the calcium pantothenate was stopped. Cortisone therapy administered during her last relapse resulted in a psychic disturbance. She is now taking calcium pantothenate and is in a remission period.

I have used calcium pantothenate alone, in doses varying from 7 to 12 gm. a day. I have used calcium pantothenate in conjunction with large doses of vitamin C, 500 mg. three times daily, and I have had a series of patients who received calcium pantothenate with vitamin E. My own impression is that the combination of vitamin C and calcium pantothenate does equally as well as vitamin E and calcium pantothenate. I would like to ask Dr. Welsh whether he had similar experience.

It is important that dextrorotatory calcium pantothenate be administered. The racemic calcium pantothenate is not as effective.

It is true that it is very expensive. The Massachusetts General Hospital supplies it at cost for our patients, thus making it easier for them financially. The dose can be gradually cut down. I have cut it down to three 500 mg. capsules three or four times a day, and found it sufficient during a period of remission.

I agree with Dr. Welsh and the previous speaker that the chronic, thickened discoid type does not respond so well, that the subacute disseminate or the generalized discoid type responds best.

I enjoyed Dr. Welsh's paper very much.

DR. CLARENCE S. LIVINGOOD, Detroit: I, too, would like to congratulate Dr. Welsh for carrying on this tedious long-term careful study. In discussing his paper, it is pertinent to emphasize that no one in this country or abroad has used his exact dosage schedule in administering these drugs for the treatment of lupus erythematosus.

We have treated a few patients in almost the same manner that he describes and for as long as 12 to 18 months. However, my discussion must be predicated by the fact that the majority of our patients received pantothenyl alcohol (Panthenol) alone, or a combination of pantothenyl alcohol or calcium pantothenate and α-tocopherol for much shorter periods of time; none of our patients received more than 800 mg. of α-tocopherol daily; the dosage of pantothenyl alcohol or calcium pantothenate was from 10 to 15 gm. daily.

It is agreed that this therapy seems to be of more value for patients who have subacute disseminate lupus erythematosus rather than the chronic discoid variety. No evidence of toxicity or a serious side-effect was noted in our series of patients, although some patients had diarrhea. In a few instances it was necessary to reduce the dose of pantothenyl alcohol or calcium pantothenate for a short period of time, in which case the number of stools decreased significantly.

We feel that this combined pantothenyl alcohol and α-tocopherol treatment described by Dr. Welsh has influenced favorably the course of several of our patients who had subacute disseminated lupus erythematosus. We have not been impressed with the results in the case of patients with chronic discoid lupus erythematosus, although as noted previously, we did not duplicate Dr. Welsh's dosage technique, and in only two cases was the treatment continued for more than one year.

In conclusion, it is my impression that this combined pantothenyl alcohol and α-tocopherol treatment seems to be indicated for some patients who have subacute disseminated lupus erythematosus. In our experience, the therapeutic results seem to be somewhat unpredictable. There are disadvantages involved in administering such treatment which makes it somewhat impractical for the majority of patients.

DR. ASHTON L. WELSH: I wish to thank the discussants for their comments. I am glad that they are attempting to treat lupus erythematosus by use of massive amounts of pantothenic acid derivatives and vitamin E.

In regard to Dr. Swartz' comment about vitamin C—I agree with him. Vitamin C enhances the antioxygenic activity of the tocopherols. In general any acid-type inhibitor will promote or energize the activity of any phenolic antitoxidant, such as tocopherol. Furthermore, vitamin C, because of its marked reducing activity, protects vitamin E in the intestinal tract.

Admittedly, the cost of these materials is high. Most of our supplies have been donated, but we have, too, a large number of patients who purchase their own medications. We have encouraged purchase wherever possible, in order to conserve donated materials for patients who cannot afford to purchase. Most patients who have had lupus erythematosus over long intervals, have already had considerable treatment expense, and are not dismayed by one more expensive treatment effort.

It is possible for a local pharmacy to buy bulk calcium pantothenate and vitamin E, capsulate, or have the materials capsulated at reasonable prices. Under one such arrangement, the price of calcium pantothenate, 0.5 gm. capsules, and of vitamin E, 100 mg. capsules, is approximately $7.50 per hundred. At that rate, cost of massive-dose therapy is not excessive.

Study of both agents is continuing and is being extended to include the part played by vitamin C in achieving favorable response; the blood levels of pantothenic acid and vitamin E in patients with lupus erythematosus, while "on" and "off" massive-dose therapy, during exacerbations, remissions, and relapses.

Study results are incomplete to date, but results which have been obtained are included in the text of this paper.

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HISTOPATHOLOGICAL DIAGNOSIS OF MALIGNANT MELANOMA

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THE CLINICAL diagnosis of a primary malignant melanoma of the skin can usually be made with a considerable degree of certainty by those acquainted with its characteristics, but even then the final diagnosis is ultimately dependent on the histological features of the lesion. In less typical cases the clinical diagnosis may be equivocal or the true nature of the lesion unsuspected before its removal, and the microscopical picture will be the sole basis for the diagnosis. Usually the microscopical features of a fully developed malignant melanoma of the skin are striking and definitive, and so no question is left as to the exact diagnosis. There are, however, instances in which the differences between an early malignant melanoma and a junction nevus may be difficult to determine, and such a case demands the most critical evaluation of all the findings by the experienced worker. Occasionally other pigmented nevi, such as the dermal nevus and the cellular blue nevus, may pose a problem. Other pigmented lesions, including the pigmented basal cell epithelioma and the pigmented verruca senilis, may sometimes be confusing clinically but as a rule are easily differentiated microscopically. One pigmented basal cell epithelioma in our series, however, was a stumbling block in diagnosis to all those who examined the sections originally. Highly anaplastic malignant lesions nonmelanomatous in origin are usually not difficult to differentiate from primary melanomas of the skin but may offer a problem of differentiation from amelanotic metastatic melanomas.

Compared with the many detailed studies on the clinical and statistical data of malignant melanomas, comprehensive studies dealing with the microscopic findings of malignant melanomas in large series of cases have been surprisingly few. Exceptions to this are the histopathological studies made on melanomas originating in the eye, of which the work of Callender, Wilder, and Ash [1] and Wilder and Paul [2] is an outstanding example. This present paper concerns itself with the microscopic features of a series of primary and metastatic malignant melanomas of the skin. From this study we have attempted to draw certain conclusions regarding those features which indicate most frequently and most definitely a malignant melanoma. The clinical evaluation of this survey was published elsewhere.[3]

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Since the completion of the work on which this paper is based, the excellent article of Allen and Spitz [4] came to our attention in which they reported on the criteria for diagnosis and prognosis in malignant melanomas. Whenever they have recorded a definite incidence of microscopical features, we have compared it with the incidence in our series.

Of the 598 cases which were reported as melanomas in the three hospitals * from which we obtained our material, 85 cases were rejected as having incomplete histories, missing biopsies, or inadequate sections. Among the 513 cases studied histopathologically, 40 cases were diagnosed as not being malignant melanomas (Table 2). Of the 473 cases which were diagnosed as malignant melanomas, 33 cases were primary in the eye, with or without metastasis, 141 were primary malignant melanomas of the skin, 38 were metastases to the skin and 261 cases were metastatic to internal organs. Autopsies were performed in 73 of these cases, and a report on the incidence of metastases to the various organs, the variation in histological pattern, and the statistics on the distribution of the primary lesions we hope to publish elsewhere.

In our study we have kept in mind the established features of malignant melanomas as they were first clearly enunciated by Unna and enlarged upon by Darier, Dawson, Miescher, and many others. We have also been mindful of the differences which were apparent between a fully developed unequivocal malignant melanoma and the features of a junctional nevus. Some two thousand junction, junction compound, and dermal nevi have been studied as the basis for this comparison. We plan to report separately upon this phase of our study.

Allen and Spitz † reported on the occurrence of a lesion in childhood which is different histopathologically from the usual pigmented nevus as well as from the malignant melanoma of the adult and named this lesion juvenile melanoma. We have seen a number of these tumors clinically and microscopically, and we tend to agree with Stegmaier and Montgomery [9] that this is perhaps a benign lesion and not a melanoma. We look upon it as probably a peculiar rapidly growing nevus with little or no pigment which occurs more commonly in children but is occasionally found in adults. Spitz has made a real contribution in separating this interesting lesion from the truly malignant melanomas with which it has been confused in the past. Cases of benign juvenile melanoma are not reported in this series, but included are two malignant melanomas which occurred before puberty, one of which was fatal.

The incidence of the main features of malignant melanomas as we found them are listed in Table 1. Studies on tissue hemorrhage, vascular dilatation, accompanying fibrosis, and other features seemed to appear increasingly unimportant as the investigation progressed, and they are omitted from this report. The presence of tumor cells in lymphatics or blood vessels in a primary lesion is highly important when seen, but it was recognized in a comparatively few cases and it is felt that, from a practical viewpoint, it is not often an aid in the diagnosis of the lesion. We

* The cases reported here were from the Los Angeles County General Hospital, The White Memorial Hospital, and the Loma Linda Sanitarium and Hospital.

† References 4 and 5.

have had no experience with the method suggested by Fitzpatrick,[8] based upon the brilliant work done by him and Becker, Lerner, and Montgomery,‡ for the histochemical demonstration of tyrosinase activity in malignant melanomas.

The incidence of the two main forms which the tumor cells of malignant melanomas take in the skin was studied, and although this information is of little value in the diagnosis of malignancy, and perhaps not in the prognosis of the lesion either, it is still of some interest. We found only 3% pure spindle cell melanomas of the skin, 30% mixed spindle and epithelioid or polyhedral cell and 57% predominantly polyhedral with a larger or smaller amount of bizarre cells. The incidence of pure spindle cell tumors in metastatic lesions was 11%, and the mixed spindle and polyhedral cell tumors were found in 20%. The incidence of spindle cell melanomas in the skin as compared with the incidence of the epithelioid type is much lower than that found for ocular melanomas as reported by Wilder and Paul.[2] The presence of the typical dendritic cell is of some importance in differential diagnosis.

TABLE 1.—*Incidence of Histopathological Features of Malignant Melanomas, Primary Lesions of the Skin—141 Cases*

	%
A. Those of primary importance	
Inflammatory reaction of the cutis	97
Mitoses	90
Single nucleus giant cells (with bizarre nucleus)	89
Pleomorphism	84
Enlargement of all tumor cells	65
Tumor cells in epidermis	51
Mitoses in epidermis	17
Tumor cells in stratum corneum or stratum granulosum	8
B. Those of secondary importance	
Melanin pigmentation	96
Hyperchromic nuclei	82
Alveolar grouping of tumor cells	81
Junctional features	72
Multinucleated cells	46
Prominence of nucleoli	45
Arborization (peripheral rete peg elongation)	45
Ulceration	42
Dysjunction of tumor cells	39
Pigment in stratum corneum	7

We also determined the incidence of the various shapes which the tumor infiltrate takes in the cutis. More than 50% of the tumors were button-shaped, a form which is seldom taken by the infiltrate of a benign nevus.

The histopathological features of malignant melanomas were divided into those of primary importance, which usually compel us to make the diagnosis of malignancy, and those of secondary importance. Such a classification is somewhat arbitrary and certainly imperfect, but it does help to stress the importance of specific findings on which a diagnosis of malignant melanoma can be made. We would also hasten to state that, even though several of the features classified as of primary importance (Group A) may individually suffice to make the diagnosis of a malignant growth, a combination of several features is usually needed to diagnose a malignant melanoma. Abnormal mitotic figures and pleomorphism in an epidermal tumor do not establish, as yet, the diagnosis of a malignant melanoma, but if they are found

‡ References 7 and 8.

in cells of the nevus type, spindle or polyhedral, combined with pigmentation, alveolar formations, and intimate junctional nevus association there can be no question about the diagnosis. Hyperchromatism of the nucleus, if marked and widespread, could perhaps be included in Group A and so also might marked prominence of the nucleoli.

ASSOCIATED INFLAMMATORY REACTION

In 97% of the primary melanomas of the skin there was an inflammatory infiltrate, lymphocytic or plasma cell in nature, which was usually mixed. This infiltrate tended to be most marked at the periphery of the lesion, often extending beyond the actual confines of the tumor. In many cases the infiltrate engulfed the entire neoplasm, while in others it was most noticeably present at the more dependent portion of the tumor. The infiltrate was rarely found scattered throughout the tumor. In intraepidermal melanomas it usually hugged the epidermis and thus might cause the mistaken diagnosis of lichen planus.

The intensity of the inflammatory reaction was moderate to marked in 82% and mild in 15% of the cases. In those cases in which the infiltrate was not found the section represented only a portion of the tumor and no further tissue was available for examination. On the basis of this study, we believe that every primary malignant melanoma of the skin is accompanied by an inflammatory infiltrate of lymphocytes or plasma cells. This inflammatory reaction is present in the earliest melanomas we have seen, in which the malignant changes involved cells in only one rete peg. Only when the tumor attains a large size does it seem that the rapidly overwhelming growth of tumor cells calls forth a steadily lessening degree of inflammatory reaction, but at the periphery of such tumors the inflammatory infiltrate persists for a long time. From a practical viewpoint, the presence of the inflammatory infiltrate is most important as an aid in diagnosis in the early lesions, which may show, as yet, a minimum of other findings indicative of malignant change. In contradistinction to the malignant melanoma, we have found an almost total absence of inflammatory reaction in junctional nevi, unless they have been severely traumatized or were the seat of a secondary infection or foreign body reaction.

Many investigators have pointed out the presence of an inflammatory reaction in malignant melanomas of the skin, but we have been surprised at the ease and frequency with which an inflammatory reaction associated with a supposedly benign junction nevus is shrugged off as of no importance and at the similar ease with which a diagnosis of a supposedly early malignant melanoma is made without the presence of an inflammatory infiltrate.

Heitzmann,[10] Unna,[11] Miescher,§ Gans,[15] Dawson,[16] and others pointed out long ago the practically unfailing presence of an inflammatory infiltrate in an early malignant melanoma. Miescher § states categorically that an inflammatory infiltrate is entirely absent in a nevus, and the context makes it clear that he is here speaking of the junctional type. Lund and Stobbe [17] found some inflammatory infiltrate in 45% of the 200 pigmented nevi they examined. In two-thirds of the nevi composing this 45% the inflammatory reaction was described as slight, and in only 15% of the 200 nevi was the infiltrate described as moderate or marked. In evaluating the report of Lund and Stobbe one must take cognizance of the fact that about 75% of the nevi they studied were dermal nevi and at least another 12% were junctional

§ References 12, 13, and 14.

compound nevi. In this group, with the high incidence of deep hair follicles and the occasional keratin cysts incident to the verrucous surface of this type of nevus, an inflammatory reaction, usually perifollicular in type, may at times be found. In our large series of dermal and compound nevi, the incidence of an inflammatory reaction is considerably less than was found by Lund and Stobbe. Stegmaier and Montgomery [9] reported an incidence of about 2% of inflammatory reactions in junction nevi in children, and in these the nevus cells were considered to be unusual. This low incidence of inflammatory reactions in junction nevi compares with our findings of an almost total absence of such reactions in uncomplicated junction nevi. Sachs, MacKee, Schwartz, and Pierson [18] recently reported that "there is no inflammatory reaction" in the junction nevus. Caro [19] stated recently that an "inflammatory reaction in a dermal nevus need not be of serious import" but that "the presence of inflammatory changes at the dermoepidermal junction of a junction nevus . . . is significant, and it calls for an extensive removal of the lesion."

The diagnostic importance of an inflammatory infiltrate in a possibly malignant melanoma is pointed out also by Caro and by Traub,[20] Lever [21] and others. Allen and Spitz || emphasize the subepidermal zone of lymphocytes in what they call the activated junctional nevus and the superficial melanocarcinoma. We question the category of "activated junctional nevi" as defined by Allen and Spitz. According to their definition, an activated junctional nevus has

> (1) the general features of nuclear anaplasia such as hyperchromatism, increase in nuclear and nucleolar size, irregular nuclear vacuolation, and mitotic figures; (2) subepithelial inflammatory reaction consisting preponderantly of lymphocytes; and (3) cytoplasmic vacuolization and fine melanin pigmentation reaching to the uppermost layers, that is, to the stratum granulosum and stratum corneum.

The only feature, according to Allen and Spitz, in which this lesion differs from a melanocarcinoma is the absence of dermal invasion. To us the criteria laid down for an activated junctional nevus are those of an intraepidermal malignant melanoma. By their own definition, they would have to examine all serial sections of such so-called activated junctional nevi in order to be certain that somewhere in the lesion no single cell had escaped from the dermal-epidermal boundary into the inflammatory infiltrate below, thus changing the diagnosis to a melanocarcinoma.

An inflammatory infiltrate associated with a junction nevus, not explainable on some other basis, to us indicates a malignant change in that lesion until proved otherwise. It is the red flag of warning that compels us to a diligent search for other definitive evidence of malignant change. On the other hand, the absence of an inflammatory infiltrate in a not too large lesion suspected of being malignant melanoma should cause serious hesitation in making such a diagnosis unless there is such an overwhelming evidence supplied by other features of malignancy that the absence of the infiltrate may be disregarded.

MITOTIC FIGURES

Mitotic figures were present in 90% of the primary melanomas of the skin and were very rare or absent in 10%. In 64% there were from one to five mitotic figures per high dry field, and in 7% there were five or more such figures (sometimes as many as 30) in each field. In practically all the cases showing mitotic

|| References 4 and 5.

figures there were some that were atypical or bizarre, and in 15% nearly all the mitotic figures were abnormal. Mitotic figures were found in the epidermis in 17% of the cases.

Miescher ¶ states that the early phase of a malignant melanoma differs from a rapidly developing nevus in two points: the presence of a massive inflammatory reaction in the cutis, and the occurrence of numerous mitotic figures in the tumor cells that have penetrated the cutis. He adds that mitotic figures outside the epidermis have as little place in a nevus as an inflammatory reaction. In 95 cases of pigmented nevi in children, Stegmaier and Montgomery [9] found only one section which showed mitotic figures. Lund and Stobbe [17] agree that mitotic figures are rare in pigmented nevi; they found mitotic figures in but 13 of the 200 nevi which

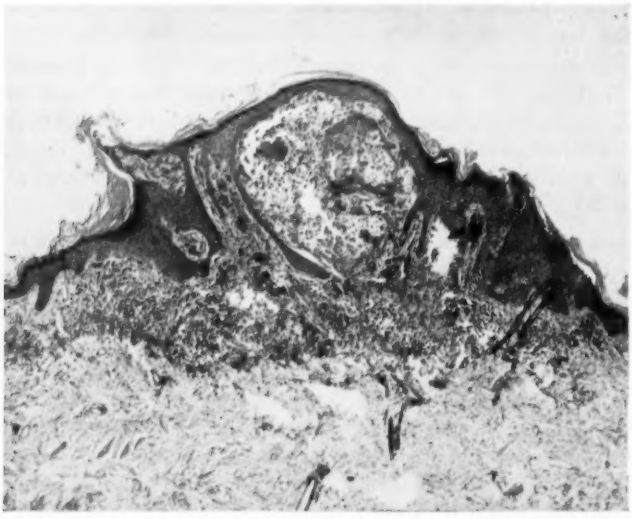

Fig. 1.—Malignant melanoma. Section shows marked acanthosis of the epidermis at the margin of the lesion as well as peripheral rete peg elongation. There is also some dysjunction of the tumor cells. Note inflammatory infiltrate at margins and base. × 80.

they examined. In these 13 cases a total of only 19 mitotic figures were present, averaging about 1.5 mitoses per section. It is also interesting that 6 of these 13 sections were from patients in the first decade of life.

Our observation that the occurrence of mitotic figures in pigmented nevi is rare is in accord with these studies. Occasionally normal mitoses may be seen in pigmented nevi, more commonly at the dermal-epidermal border or in the area immediately adjoining, but the incidence is very low (probably less than 3%), and there is usually only one mitotic figure in an entire section. Compared with this lack of mitoses in benign nevi there is a high incidence of many mitotic figures in malignant melanomas. For this reason, the occurrence of even a few mitoses in a possible malignant melanoma should be presumptive evidence for its malignancy, to be corroborated by other findings. If there are many mitoses in such a section, the

¶ References 12, 13, and 14.

diagnosis of a malignant melanoma becomes practically a certainty, even in the absence of other criteria. In the so-called juvenile melanoma, which might be cited as a possible exception, mitotic figures have been very few in the cases which we have studied, and Allen and Spitz [4] seem in agreement with this when they state that "one or even several mitotic figures are found not infrequently." Even though the presence of a large number of mitotic figures in a possible malignant melanoma might force us to make a diagnosis of a malignant tumor on this basis alone, in almost every instance in which appreciable numbers of mitotic figures are found there are associated with this such other features of malignancy as to make the diagnosis inescapable. One of these associated diagnostic features is the presence of atypical and bizarre mitoses, which are never seen in a benign nevus.

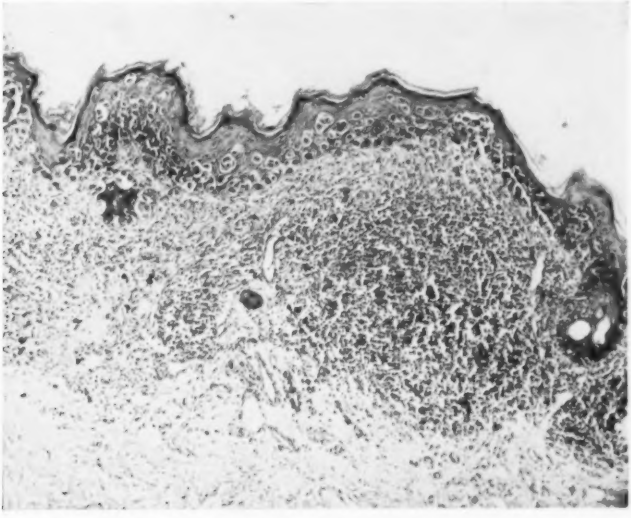

Fig. 2.—Malignant melanoma. Many tumor cells in epidermis with beginning penetration into dermis. Marked inflammatory infiltrate. × 82.

SINGLE NUCLEUS GIANT CELLS

The 89% incidence of single nucleus giant cells in our series is almost identical with that of mitotic figures. This similarity is, however, somewhat deceiving, for in many cases in which the number of mitotic figures is low the giant cells with bizarre nuclei are abundant. It has been suggested that these large cells with monstrous nuclei are, in reality, the product of extremely abnormal and abortive mitotic activity, and we are inclined to subscribe to this view. Such giant cells may have 20 times the diameter of the average nevus cell; they may be round, oval, spindle-shaped, multiangular, or exceedingly irregular, with an abundance of finely granular or homogeneous cytoplasm. The nucleus is proportionately large, twisted, frayed, or fragmented, sometimes apparently having undergone abnormal division into a bizarre multinucleated cell. Usually the nucleus is markedly vacuolated and has a prominent chromatin network. Occasionally the entire nucleus is black, as if it were a huge mitotic figure. Such giant cells are never seen in benign nevi or in the so-called juvenile melanoma; they are primary evidence of malignant change.

Unna [11] clearly described these bizarre giant cells and separated them from the multinucleated giant cells, which may also be found in the same sections, but which are far less important from a diagnostic standpoint. Small single nucleus giant cells (if such a contradiction of terms may be permitted) as are seen in so-called juvenile melanomas show no bizarre nuclei and their nuclei show an absence or paucity of vacuolization, which is so prominent in the bizarre nucleus of the giant cells of malignant melanomas. We feel that the presence of such single nucleus bizarre giant cells in a lesion of nevus origin forces us to make the diagnosis of a malignant melanoma. Somewhat similar giant cells are found in other highly malignant and anaplastic lesions, such as liposarcoma, and in metastatic nonpigmented melanomas such differentiation may be exceedingly difficult.

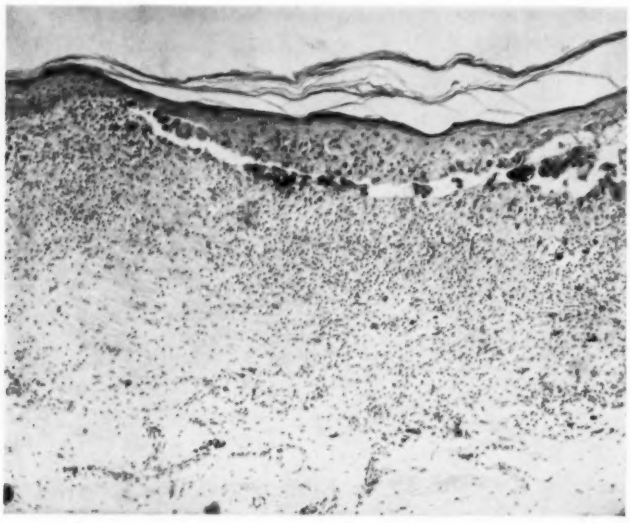

Fig. 3.—Malignant melanoma. Tumor cells in epidermis, with loosening of cells at junctional border. Considerable inflammatory infiltrate in upper cutis. × 76.

PLEOMORPHISM

A noticeable variation in the size and shape of the tumor cells is seen in 84% of the primary malignant melanomas of the skin. Usually this is associated with varying hyperchromatism of the nucleus. Dawson [16] has pointed out, regarding the melanoma cells which have invaded the dermis, that their polymorphism may be their most striking feature. In some cases it may indeed be the only feature indicating malignancy, and in such cases it is usually present in an extreme degree. Gans [15] designates the pleomorphism of melanomas as extraordinary. Allen and Spitz # report a 37% incidence of pleomorphism (3 to 4 + intensity) in the lesions from fatal cases of malignant melanomas and an incidence of 17% in those which survived. A slight degree of pleomorphism may sometimes be seen in the most superficial cells of a dermal nevus, but the limits of variation are small.

References 4 and 5.

SIZE OF TUMOR CELLS

In 65% of the primary melanocarcinomas of the skin there was a general enlargement of all the tumor cells to such a degree that the increased size was immediately noticeable. Unna,[11] Johnston,[22] Miescher,[13] and many others have called attention to the large size of tumor cells in malignant melanomas. Some tumor cells are only slightly larger than the larger nevus cells in the dermis, but to find a melanoma almost exclusively composed of such cells is uncommon. In those primary tumors in which a considerable portion of the tumor cells are of the small variety, there are nearly always areas in which some large tumor cells occur and mitotic figures tend to be abundant in this type of melanoma. The larger of the ordinary nevus cells in the upper part of the dermis usually measure about 10 μ in diameter. The small tumor cells are only slightly larger, 12 by 13 μ. The

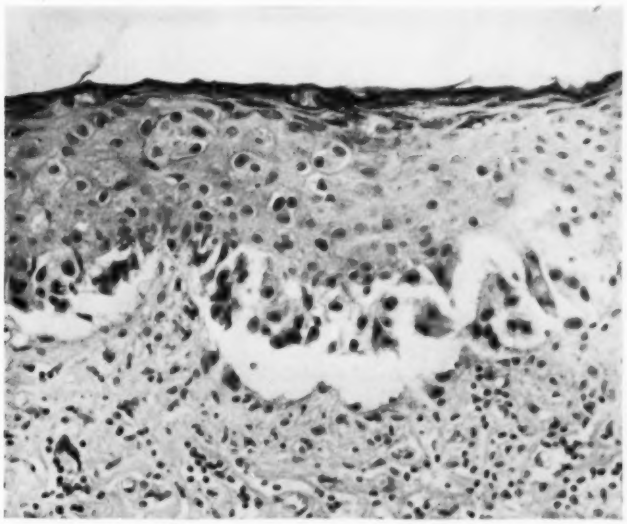

Fig. 4.—Malignant melanoma. Higher magnification of another portion of same lesion as Figure 3. × 224.

average tumor cells in most tumors measure 20 μ or more in diameter up to the single nucleus giant cells of up to 200 by 230 μ.

TUMOR CELLS AND MITOSES IN THE EPIDERMIS

In 51% of the primary nevocarcinomas there were tumor cells in the epidermis. Mitotic figures were found in 17% of the cases, and actual tumor cells in the stratum granulosum and stratum corneum were noticed in 8% of the melanomas. Tumor cells in the epidermis generally exceeded in size the average tumor cell in the dermis and are larger than the nevus cells found in the junction nevus, which was also noted by Stegmaier and Montgomery.[9] Cells measuring 55 by 60 μ are not uncommon, and larger ones than these are encountered. Most of the tumor cells tend to occur in the basal cell portion of the epidermis, but single cells and groups of cells may appear in the more superficial layers. The tumor cells can be

differentiated from the nevus cells not only by their larger size but also by the greater variation in shape, the variation of the chromatin content of the nucleus and the occurrence of occasional mitoses, which may be abnormal. In some instances practically the entire epidermis was filled with large tumor cells, and it seems that in time, as the tumor cells are lost from the stratum corneum and through the dermal-epidermal junction, the epithelial covering is reduced to a one-cell thickness, which may rupture and produce a small ulcer.

Dawson [18] noted the increase in cytoplasm of the tumor cells in the epidermis, as well as the hyperchromatism of the nucleus, and the presence of polymorphism and infrequent mitoses. Lever [21] makes the invasion of tumor cells in the upper

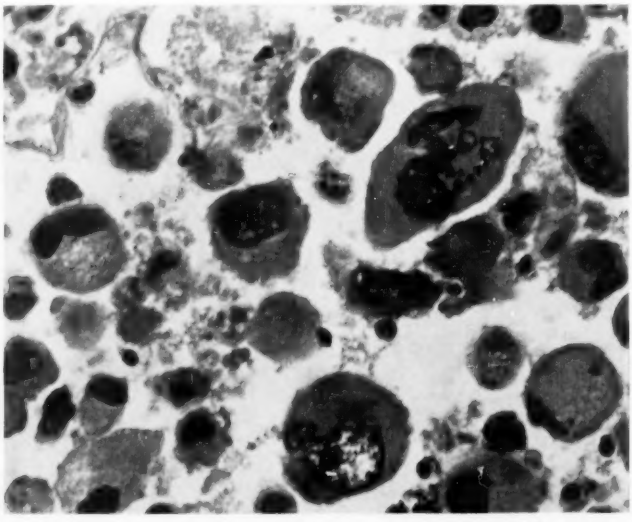

Fig. 5.—Malignant melanoma. Single nucleus giant cells with bizarre nuclear patterns. Vacuolation is usually more pronounced. Hyperchromatism is marked. × 560.

part of the epidermis one of the absolute criteria of a malignant melanoma, and we are in agreement with that dictum.

MELANIN PIGMENTATION

Melanin pigment was recognizable in 96% of the primary cutaneous malignant melanomas. The pigmentation was slight in 23%, moderate in 65%, and marked in 8%. Since most junction nevi have pigment in the cells at the dermal-epidermal border, melanin must be present elsewhere in a nevocarcinoma to be of diagnostic aid. In addition to the lower part of the epidermis, we found melanin pigmentation present most frequently at the periphery of the tumor infiltrate and three times as frequently in the upper portion of the tumor as at its lower edge. In 24% of the cases the melanin was scattered throughout the tumor; in 20% it was in the upper part, and in 6% it was located mainly at the border of the lesion. Marked pigmentation of the stratum corneum was noted in 7% of the cases.

Miescher * believes that increase in pigmentation is one of the earliest changes in the malignant melanoma cell and associated with this is the possibility of the appearance of the pigmented cell in the stratum corneum. In 1888 Heitzmann [10] had noted the importance of melanin pigment in the uppermost layer of the epidermis in this tumor, and many authors have since emphasized this point. We observed, however, that in some benign junction nevi melanin pigment may also be carried to the stratum corneum.

Melanin pigmentation in a melanocarcinoma, if properly identified, is of diagnostic aid, particularly in differentiating the tumor from nonmelanomatous lesions. Since pigmented nevi show the presence of melanin chiefly at the dermal-epidermal

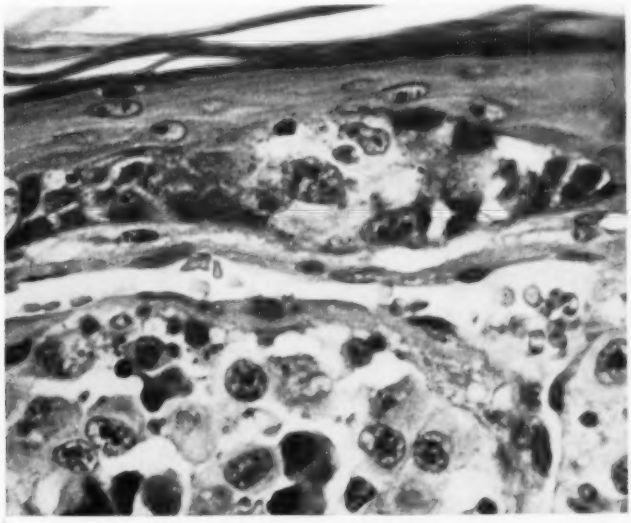

Fig. 6.—Malignant melanoma. Tumor cells in epidermis as well as cutis. Tumor cells show marked pleomorphism and hyperchromatism, prominent nucleoli, vacuolation of some nuclei and a tendency toward dissociation of the cells. × 620.

junction and in the immediately adjoining area, the finding of a fair amount of pigment elsewhere, such as at the periphery, at the lower border or throughout the tumor, is suggestive of a possible malignant state, but no more than that. Massive pigmentation is rarely seen in a dermal nevus, and such a finding should be a warning to bleach the section so that the cell detail may be studied. Allen and Spitz,† who found pigmentation in 79.2% of their cutaneous melanomas, noticed the presence of melanin in only 54.7% of the primary melanomas of the mucous membranes, and they point out that if reliance is placed on pigmentation in the diagnosis of melanomas about half of those originating in the mucous membranes will be missed.

* References 12, 13, and 14.

† References 4 and 5.

HYPERCHROMATISM OF NUCLEI

As would be expected from the features already described, the incidence of hyperchromatism of the nucleus should be high in melanomas. In 82% of our cases this fact was immediately noticeable. In most sections this hyperchromatism varied from cell to cell, thus contributing to the pleomorphism of the tumor. In many instances it was present quite uniformly throughout the section, while in others there were areas of hyperchromatism which alternated with those showing very little of this feature. An occasional nevus cell in a pigmented nevus may reveal hyperchromatism, but this is insignificant compared to what is seen in the malignant lesion. Johnston [22] has well stated that "a malignant tendency may be suspected when nuclear hyperchromatism becomes prominent."

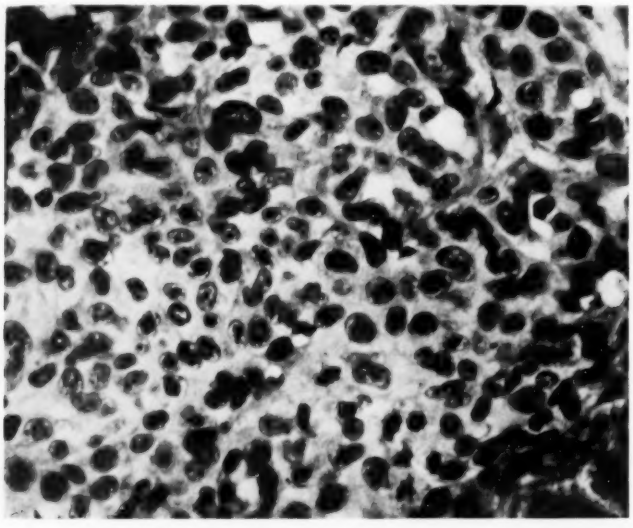

Fig. 7.—Malignant melanoma. Marked pleomorphism and hyperchromatism. Several mitotic figures are present. × 240.

ALVEOLAR GROUPING

Heitzmann [10] called attention to the alveolar architecture of malignant melanomas as seen in the cutis, and many investigators have emphasized this fact since that time. We found alveolar grouping of tumor cells present in 81% of the primary lesions. In some of these almost the entire tumor was alveolar in nature, while in others there were only a very few alveolar groupings. Such structure, of course, is not an indication of malignancy in itself, since benign nevi may have a similar architecture, but its presence may be of great help in differentiating an amelanotic melanoma from other tumors. Besides adenocarcinoma, other malignant tumors may rarely simulate an alveolar grouping. In visceral metastases, where the problem of differential diagnosis is a much greater one if melanin is absent, there was evidence of alveolar structure in 83% of the cases. In the 20 cases of Miescher [13] 16 (80%) showed alveolar formations, which is practically identical with our findings.

JUNCTIONAL FEATURES

Evidence of a junction nevus associated with a malignant melanoma was found in 72% of the lesions. This, of course, is in support of the now generally accepted belief that most melanocarcinomas of the skin originate in a junction nevus, as advocated by Traub and Keil.[23] This finding has some practical value since it may be an aid in recognizing an amelanotic melanoma without alveolar groupings. It is also helpful in differentiating a primary cutaneous nevocarcinoma from a metastatic one, as Allen [24] has pointed out. Metastasis is unlikely to form underneath a junction nevus and metastatic tumor cells seldom invade the overlying epidermis, though they may erode through it. In the primary malignant melanoma, as Lever [21] has also noted, junctional activity may be much greater and more irregular than

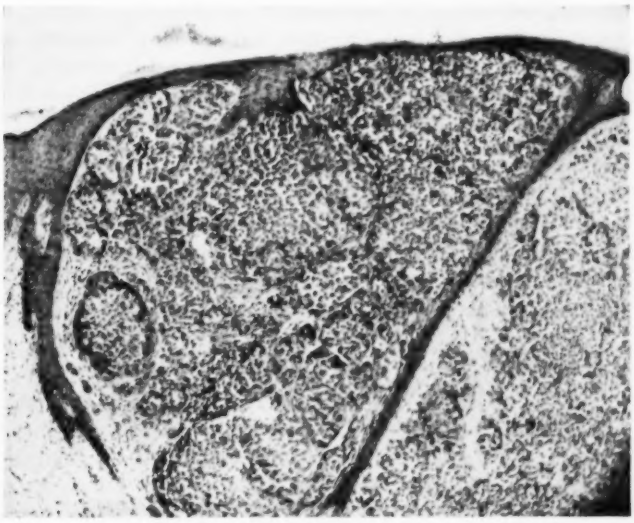

Fig. 8.—Malignant melanoma. Marked rete peg elongation with thinning of the epidermis overlying the tumor. Tendency toward alveolar formation of tumor cells can be noted. × 64.

in the benign junction nevus. Ulceration may destroy the evidence of a junction nevus, but, as is shown in our series, it is seldom able to do this completely. Berkheiser and Rappoport [25] found junctional proliferation marked in nine out of 12 malignant melanomas, and in three in which the junctional changes were slight or absent there was marked acute ulceration.

MULTINUCLEATED AND CLUMPED CELLS

The presence of multinucleated giant cells in melanocarcinoma was described by Unna,[11] and this has been noted by many authors since. We found a 46% incidence of multinucleated cells and a 33% incidence of clumped cells. As both of these cell forms occur in benign nevi, their presence as such is not diagnostic of malignancy, but they are seen much less frequently and in fewer numbers in benign nevi. This multinucleated cell has a number of small nuclei, usually deep-staining, three to eight or more in number, which are most often located in a circle at the

periphery of the cell. Sometimes, however, they are found at one side and are occasionally scattered throughout the entire cell. This is a large cell, usually larger than the multinucleated cell in the benign nevus, but it never approaches the size of the bizarre single nucleus giant cell.

The clumped cells are sometimes difficult to distinguish from the multinucleated giant cells, but they seem rather a compression of a number of smaller tumor cells into a closely packed group, with the disappearance of most of the cytoplasm. Six nuclei appear to be the average number included in this cell form, but as many as 16 may be seen in one group. Lund and Stobbe [17] have recognized these two types of multinucleated cells. They report an incidence of 45% of these cells in their series of 200 pigmented nevi, but in more than half of these the number was infrequent. Berkheiser and Rappoport [25] found multinucleated forms extremely scarce in junctional nevi, but they were prominent in the dermal part of compound nevi. In malignant melanomas they noted multinucleated cells in moderate numbers in eight of their 12 melanomas, and they stated that the nuclei resembled those of the surrounding tumor cells. In the other four melanocarcinomas they detected only a few multinucleated cells.

PROMINENCE OF NUCLEOLI

Compared with the benign nevus, it was found that in 45% of the sections the nucleoli were noticeably more prominent in malignant melanomas. Many of the tumor cells had two or three nucleoli. Associated with this was an increase in the prominence of the chromatin network of the nucleus, and there was a tendency for the chromatin to be packed at the periphery.

ARBORIZATION

Early in the course of our study we were impressed with the frequency with which we encountered a peculiar elongation of the rete pegs at the periphery of the melanocarcinoma. In many of the tumors there seemed to be an actual attempt of the rete pegs to engulf the newly formed tumor. Heitzmann [10] described an enlargement of the rete pegs, both in length and in width, even at some distance from the tumor. Johnston [22] pointed out the hyperplasia which produced great elongation of the rete pegs, bringing them into close apposition with the tumor. He also mentions correctly that rete peg elongation is seen at times in benign nevi but that it is easy to differentiate this elongation from that which occurs in the malignant melanoma. We also believe that the elongated, thinned, compressed rete pegs often seen as narrow strands dipping downward between compressing walls of tightly packed nevus cells in the center of a benign nevus are easily differentiated from the peripheral rete peg elongation seen in the nevocarcinoma. The incidence of this peripheral rete peg elongation or arborization was 45%.

ULCERATION

Uncomplicated pigmented nevi do not show ulceration, and the clinical or microscopical evidence of such a process in a nevus is suggestive of malignant change. Histopathological evidence of ulceration was found in 42% of the primary nevocarcinomas of the skin. The ulceration varied from a minimal break in the epidermis to an almost complete loss of the epithelial covering, with massive destruc-

tion of the tumor itself. As mentioned before, extensive ulceration may obliterate the evidence of a preexisting junction nevus and thus make the differential diagnosis between a primary and a metastatic melanoma in the skin much more difficult.

DYSJUNCTION OF TUMOR CELLS

Unna [11] called attention to the tendency of intraepidermal nevus cells to separate or loosen themselves from adjoining cells prior to their dropping off into the cutis. Kaufmann-Wolf [26] uses the terms disorganization and dissociation; Darier [27] describes it as segregation; Miescher [14] uses the word *Auflösungsprozess* (separation or loosening), and Gans [15] employs the word acantholysis. Dawson [18] describes the process as one of detachment or individualization and applies it to melanocarcinoma. Miescher also emphasizes that this process, though of normal occurrence in the benign pigmented nevus, becomes much more pronounced in the malignant melanoma. We have observed a tendency of the tumor cells in nevocarcinomas

TABLE 2.—*Diagnoses of Forty Cases Microscopically Not Melanomas*

	No. of Cases
Junction nevus	7
Blue nevus	7
Dermal nevus	5
Cellular blue nevus	4
Junction compound nevus	3
Basal cell epithelioma	3
Dermatofibroma	2
Seborrheic keratosis (verruca senilis)	2
Adenocarcinoma	1
Kaposi's sarcoma	1
Lymphoma	1
Lichen planus	1
Hidradenoma	1
Anaplastic squamous cell carcinoma	1
Pyogenic granuloma	1

to show this dissociation, or dysjunction as we have termed it, not only in the epidermis or immediately adjacent to it but also almost anywhere in the tumor, including visceral metastases. It was present in 39% of the primary lesions and is seen most commonly in the upper portion of the dermis and at the periphery of the tumor; but, as stated before, it may occur anywhere. The separation or individualization of the cells may be present in only a small area, or the larger part of the tumor may be involved. A mild degree of dysjunction can be seen in some compound junction nevi, but the separation of the individual cells is not as marked as in malignant melanomas, nor is it as widespread.

DIFFERENTIAL DIAGNOSIS

Table 2 lists the pathological diagnoses of 40 cases which had been clinically diagnosed as malignant melanomas. Some of these were originally diagnosed by the pathologist also as nevocarcinomas. It will be noted that pigmented nevi comprise 26 of the 40 cases. It is clear that the differentiation of pigmented nevi from malignant melanomas is the chief problem in differential diagnosis. Among the cases which were clinically not diagnosed as malignant melanomas but which were found to be so on microscopical examination, pyogenic granuloma, squamous cell

carcinoma and pigmented nevus were the three most frequent diagnoses. We have mentioned in the discussion of the individual diagnostic criteria their importance in differentiating nonmelanomatous lesions, especially the junction nevus. The cellular blue nevus of Allen,[24] which is identical with the *neuro-nevus bleu* of Masson,‡ may look quite formidable because of its heavy melanin pigmentation in the dermis, but the real features of malignancy are absent. In our series is one case of a malignant melanoma originating in a cellular blue nevus, and a second case which probably originated in such a lesion.

The other lesions in Table 2 may also show pigmentation clinically, and, for this reason, were probably confused with malignant melanomas. If the presence of the pigment is disregarded, these lesions are distinct enough to make a differential diagnosis quite simple in most cases. There are times when an anaplastic carcinoma, a lymphoma, or an adenocarcinoma may offer a real problem in differentiation from a metastatic melanoma, but from a primary melanoma this is usually not difficult.

Metastatic melanoma in the skin can usually be differentiated from primary lesions by the absence of tumor cells in the epidermis (although in rare instances they may penetrate here), by the absence of junctional features, and by the presence of a small zone of connective tissue between the tumor infiltrate and the epidermis. It is stated that an inflammatory infiltrate does not occur with a metastatic lesion, and we agree that this is so in the majority of cases. In 24% of the metastatic lesions of the skin there was some inflammatory infiltrate present, though only rarely was it as marked as is usually seen in a primary lesion.

SUMMARY

In a study of 179 cases of malignant melanomas of the skin the incidence of various diagnostic criteria was determined. The diagnosis of a primary malignant melanoma of the skin can be made if the following criteria are present in association with junctional features: (1) an inflammatory infiltrate at the periphery of the lesion; (2) more than an occasional mitotic figure; (3) giant cells with a single bizarre nucleus; (4) marked pleomorphism; (5) general enlargement of all tumor cells; (6) tumor cells and mitoses in the epidermis.

If associated with a junction nevus, usually one or two of these features are necessary to arrive at the diagnosis of a malignant melanoma. In most instances three or more of these factors will be present in a primary malignant melanoma. Criteria which we have classified as of secondary importance may, nevertheless, be essential in making a diagnosis in a given instance, and they are always of value as supplementary evidence. These criteria are melanin pigmentation, hyperchromatism of the nucleus, prominence of the chromatin network and of the nucleoli, alveolar grouping of the tumor cells, junctional features, multinucleated giant cells, peripheral rete peg elongation, ulceration, and dysjunction of the tumor cells.

The junction or junction compound nevus presents the chief problem in the differential diagnosis of the malignant melanoma. In the uncomplicated state of this nevus, we find no inflammatory infiltrate and practically no mitotic figures, while in the primary melanoma of the skin the inflammatory infiltrate is always present

‡ References 28 and 29.

and mitotic figures nearly always present. Single nucleus giant cells with bizarre nuclei, which are present in 89% of malignant melanomas, are never seen in benign nevi.

1930 Wilshire Blvd. (57) (Dr. Couperus).

ABSTRACT OF DISCUSSION

DR. SAMUEL W. BECKER JR., Washington, D. C.: The authors should be congratulated for their careful tabulation of the microscopic findings in melanomas, and they have, indeed, been fortunate to be able to study so many of these lesions.

Because of the number of articles appearing on nevi and melanomas in the recent literature, I should like to digress just a moment. Nevi and melanomas are lesions which exhibit marked variation in the microscopic picture from area to area. Since serial sectioning of all these lesions is impossible, the study of microscopic slides is essentially a sampling procedure.

As the quality control engineers will tell you, sampling studies can be compared statistically only if the samples are equivalent. If one investigator, for instance, studies mitotic figures in nevi in children and observes many sections from each nevus while another investigates mitotic figures in nevi in adults but observes only one section from each nevus, each will arrive with a percentage of nevi exhibiting mitotic figures, these percentages cannot have the same significance, since in the first study more material was examined than in the second. There is a tendency to study more histological sections in the bizarre than the routine lesions.

There should also be a standardization of staining; for instance, if all statements as to presence or absence of melanin were made on the basis of silver nitrate stain, there would be more uniformity. If the authors who are doing this type of study could agree on a standard sample, such as one section through the middle of the lesion and one section every 2 mm. along the entire lesion, it would make the reports much better as far as the statistical analysis goes.

The authors have presented an excellent tabulation of the pathological features seen in melanomas. Consideration of all the features of a lesion is usually necessary to diagnose a melanoma, and the authors have emphasized the findings that are the most important.

I should like to ask Dr. Couperus whether he has been able to predict the prognosis on the basis of the anaplasia seen in the sections and what the percentage of correct clinical diagnosis in the melanomas of his series was?

DR. MOLLEURUS COUPERUS, Los Angeles: I want to thank Dr. Becker for his interesting discussion.

In the study of these tumors, primary and metastatic melanomas of the skin, we have had an average of about five sections per tumor. Some of the cases had as many as 20 slides, and in the older sections in which the block was gone we only had one slide. Some of these slides had two or more sections on them, and five sections was probably the average number of sections we studied per case.

I agree with Dr. Becker that it would be very desirable if we could have a uniform procedure in arriving at percentages in such studies as these, and perhaps a way can be worked out in which a certain minimum number of sections per tumor will form the basis of the statistical data.

Concerning the prognosis in the lesions which were exceedingly anaplastic, we have not yet broken this down into a percentage, but our impression is that the anaplastic lesions metastasize much earlier and much wider than those which are less anaplastic.

I am not able at this time to answer the question regarding the percentage of correct original clinical and histopathological diagnoses. This will be reported in a subsequent paper.

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ECTOPIC GASTROINTESTINAL MUCOSA IN FORM OF UMBILICAL POLYP

Report of a Case

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PHILADELPHIA

AND

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BRUSSELS

ACCORDING to a report by Vernon in 1951,[1] polypoid or papillomoid lesions of the umbilicus are rare. His case represented the 15th recorded in the literature. Our patient, a boy of 3 months, had a congenital umbilical polyp persisting after the healing of the umbilical cord and presenting clinically the appearance of a granuloma pyogenicum, but found histologically to be ectopic gastrointestinal tissue, presumably a residue of the omphalomesenteric duct.

Inasmuch as the majority of congenital polyps in this region have been found to be associated with congenital abnormalities in the closure of the urachal or omphalomesenteric ducts, and also because they are sometimes associated with fistulous connections between the polyp and the gastrointestinal tract or the urinary tract, it was thought worthwhile to bring this rare anomaly to the attention of dermatologists.

REPORT OF CASE

R. M., a white child, aged 3 months, was found completely normal on examination, with the exception of a solitary red moist polyp in the umbilicus measuring approximately 5 mm. in diameter. The surface was covered with a glary mucoid secretion but was devoid of crust or hemorrhagic or purulent discharge. The skin about the umbilicus was not inflamed or eroded.

The child, born of normal spontaneous delivery, had a normal history except that the polyp described above was found after the healing of the cord and remained unchanged until the time of examination. There was no dimple or dell in the center of the lesion, nor could a fistulous tract be discovered. The lesion was excised for histologic examination, and the base was lightly electrodesiccated. The wound healed well, and the child made an uneventful recovery.

The microscopic findings (hematoxylin-eosin stain) reported by one of us (H. B.) were as follows: This section of skin shows an elevated epithelial lesion (Fig. 1 and 2) resting on a base of fibrous tissue. The squamous epithelium in the summit of the lesion is replaced by mucous membrane. This is sharply delimited from the surrounding squamous epithelium. There is a stroma of loose fibrous tissue, which contains numerous dilated capillaries and many simple tubular glands of mucous type such as is seen in the gastric mucosa. Some of the cells contain red granules (acid cells? Paneth cells?) (Fig. 3). There is also a certain amount of leucocytic infiltration at one end of the mucous membrane.

From the Departments of Dermatology, School of Medicine and Graduate School of Medicine, University of Pennsylvania.

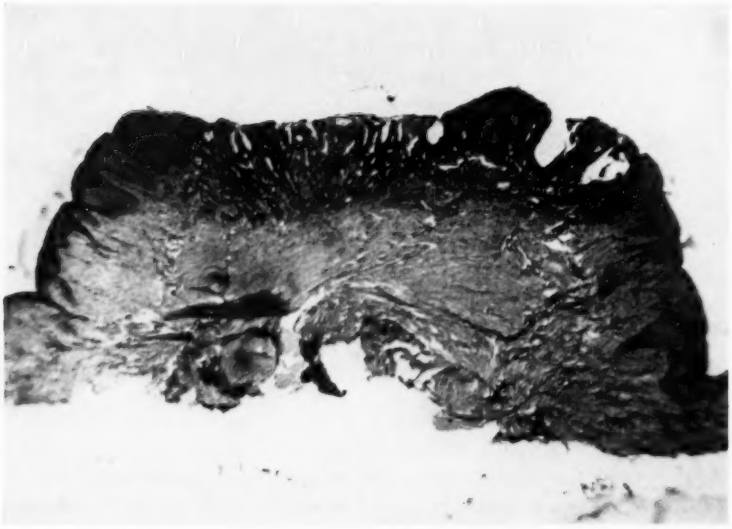

Fig. 1.—Gross view of umbilical polyp in cross section (× 20) showing collection of mucous glands in the center of the lesion.

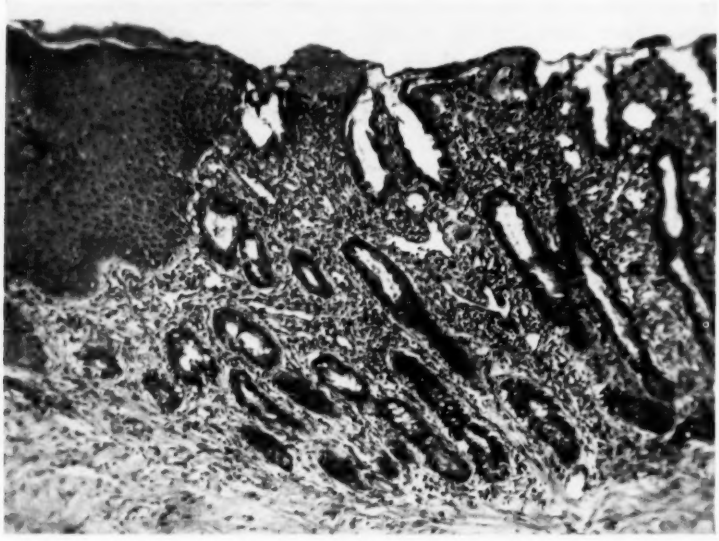

Fig. 2.—Higher power showing mucous glands in proximity to squamous epithelium; × 93.

The sections were also examined by Dr. R. C. Horn, who made a diagnosis of umbilical polyp with histologic appearance suggesting origin from the small intestine. Dr. Hamilton Montgomery also believed that it represented an embryonal rest of intestinal tissue. Dr. Llyod Ketron and Francis Ellis.* thought the lesion might be nevus syringocystadenomatosus papilliferus. Dr. Fred D. Weidman felt that this was a "remarkable example of ectopic mucous membrane having its origin in a gastrointestinal tract."

COMMENT

Cullen,[2] Puccini and Nocentini,[3] and McFarland [4] have discussed in detail the congenital anomalies involving the umbilicus. Trimingham and MacDonald [5] have

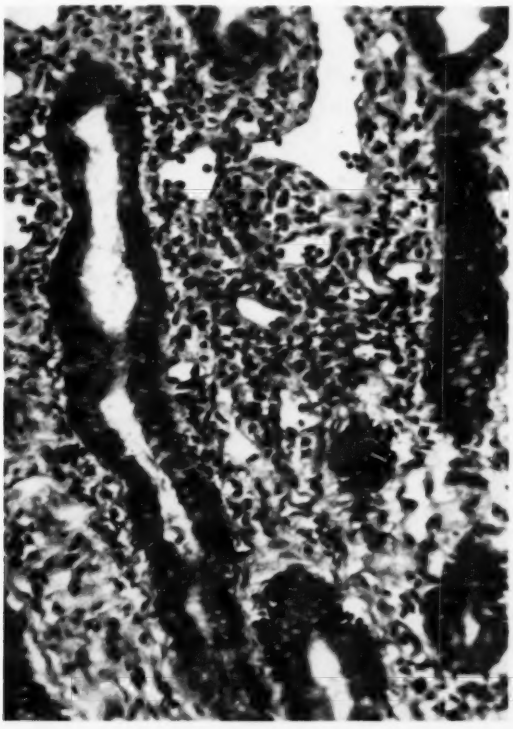

Fig. 3.—Higher power view of mucous glands; × 283.

included in their listing alimentary, urachal, and vascular anomalies. The gastrointestinal anomalies will vary from a completely patent omphalomesenteric duct, sometimes called an umbilical enteric fistula, through a partially patent duct to mere mucosal remnants at the umbilicus [6] (Fig. 4 and 5). The case of the child presented here corresponded to this last category. Similar anomalies are also found involving the urachal duct. Occasionally polypoid or tumor-like lesions are found at the umbilicus which represent persistent omphalomesenteric or urachal blood vessels.

* Ketron, L., and Ellis, F.: Personal communication to the authors.

Other abnormalities include hernias and endometriosis. In addition to the above lesions one may of course find papillomata and polyps of an etiology similar to that found in other parts of the skin, including epithelioma, fibroma, sarcoma, dermoid cysts, and granuloma pyogenicum.

Our clinical diagnosis was granuloma pyogenicum. Because of a possibility of a ductal connection between the lesion itself and the gastrointestinal tract or the urinary tract, the importance of considering the correct clinical diagnosis before excision is quite apparent.

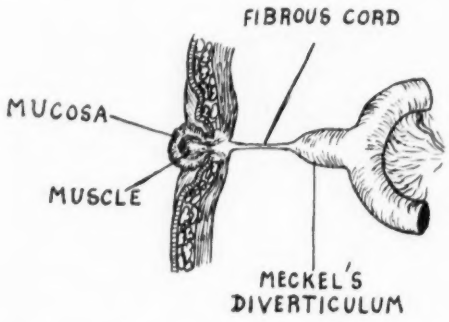

Fig. 4.—Diagrammatic representation to indicate the relationship between the obliterated omphalomesenteric duct (fibrous cord), Meckel's diverticulum, and an umbilical polyp. Modified from Cullen.[2]

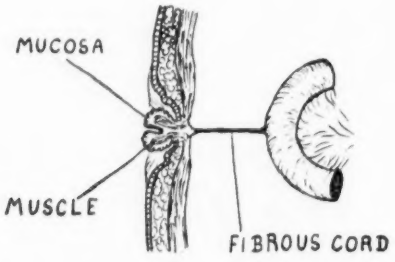

Fig. 5.—Diagram to show the remnant of the lumen of the omphalomesenteric duct in the center of an umbilical polyp. Modified from Cullen.[2]

Vernon found his case of papilloma of the umbilicus to be of epithelial origin. He, however, first ruled out gastrointestinal and urinary tract connections by the serial administration of carmine red chalk and methylene blue by mouth.

SUMMARY AND CONCLUSIONS

A case is reported of ectopic gastrointestinal mucosa presenting at the umbilicus in the form of an umbilical polyp in a child of 3 months and remaining as a remnant after the healing of the umbilical cord. This presumably represented the residuum of the primitive vitelline, or omphalomesenteric, duct. Inasmuch as it presented

some of the features of granuloma pyogenicum and also because polyps of this clinical appearance sometimes connect by means of fistulas with the gastrointestinal or urinary tract, the differential diagnosis is of real importance.

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ANTIBIOTIC AND SULFONAMIDE IN VITRO STUDIES IN PUSTULAR ACNE VULGARIS

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PATIENTS with therapeutically resistant acne vulgaris are still commonly seen. Occasional patients fail to show adequate response in spite of intensive treatment with dietary restrictions, local agents, removal of infectious foci, roentgen therapy, comedone expression, endocrinologic agents, vaccine therapy, and other acceptable remedies. Clinically, it has been shown that the administration of one of the sulfonamides or an antibiotic may cause decided improvement in some instances of pustular acne.[1] The decision as to which of these therapeutic agents the clinician should try first becomes rather significant. In an attempt to answer this problem, two of the methods for carrying out in vitro sensitivity studies have been utilized comparatively in this investigation. One of these is designated the paper disc method and technically is easily performed. The other method consists of tube serial dilution tests and involves considerably more time and effort in its execution. Only patients with the pustular type of acne vulgaris were considered, and the following phases were investigated: (1) isolation and identification of the bacteria present in the acne pustule; (2) testing the organism in vitro against various sulfonamide and antibiotic agents by the paper disc and tube serial dilution techniques, and (3) subsequent administration of the most effective in vitro drug to patients with recalcitrant pustular acne vulgaris.

PAPER DISC METHOD

Procedure.—Pustules of each acne patient were incised, and a direct smear was made on a glass slide. The smears were stained with Gram's stain and examined microscopically. Cocci were the only organisms seen. At the same time a sterile swab with some of the purulent material was inoculated into a tube of thioglycollate broth. The broth inoculum containing the swab was incubated overnight. After this period the entire surface of a blood agar plate was streaked with a loop from the broth inoculum. The plate was incubated 30 to 60 minutes in order that the surface might dry; then with flamed, cooled forceps five antibiotic * and three

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* The Bacto Sensitivity Disks were manufactured by the Difco Laboratories, Inc., Detroit 1, Mich. The concentrations of the discs used were as follows: penicillin 1 unit; chlortetracycline 30 γ; chloramphenicol 30 γ; oxytetracycline 30 γ; dihydrostreptomycin 1 γ.

sulfonamide † discs were placed on the inoculated surface, 1 to 1½ in. (2.5 to 3.8 cm.) apart. The plate was incubated for 18 hours and then examined for growth. The organisms grown were identified by colony and microscopic characteristics. The in vitro sensitivity of the organism was estimated by the extent of the zone of inhibition around the antibiotic and sulfonamide discs.[2]

Sensitivity of Organisms by Paper Disc Method.—One hundred forty-two consecutive acne vulgaris patients with pustular lesions were examined, and a culture was made. The predominant organism was hemolytic Micrococcus pyogenes variety albus (Staphylococcus albus) in 106 patients, nonhemolytic M. pyogenes var. albus in 20, hemolytic M. pyogenes var. aureus (Staphylococcus aureus) in 3 patients, and nonhemolytic M. pyogenes var. aureus in the remaining 13 patients.

Sixty-nine of the 142 organisms were more sensitive to penicillin than to any of the other agents used. Chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and chloramphenicol (Chloromycetin) were next in order of effectiveness. Twenty-two of the 142 organisms were resistant to penicillin. Dihydrostreptomycin was the least effective of the antibiotic agents used; 59 of the 142 bacteria tested were found to be resistant to dihydrostreptomycin. Sulfamerazine, sulfadiazine, and sulfisoxazole (Gantrisin) were ineffective as tested in this investigation. The limitations in carrying out satisfactory practical laboratory methods for testing bacterial sensitivity to the sulfonamides have been recognized.‡

TABLE 1.—*Interpretation of Width of Zones of Inhibition Surrounding Antibiotic or Sulfonamide-Saturated Paper Discs in Terms of Sensitivity of the Organism to the Drug* [2]

	Very Sensitive *	Moderately Sensitive †	Slightly Sensitive ‡	Resistant §	Total
Penicillin	90	12	18	22	142
Chlortetracycline	12	104	22	4	142
Oxytetracycline	6	108	19	9	142
Chloramphenicol	3	92	40	7	142
Dihydrostreptomycin	0	3	80	59	142
Sulfamerazine	0	1	7	134	142
Sulfadiazine	0	0	3	139	142
Sulfisoxazole	0	0	2	140	142

* Over 20 mm. interpreted as very sensitive.
† From 10 to 20 mm. interpreted as moderately sensitive.
‡ From 0 to 10 mm. interpreted as slightly sensitive.
§ No inhibition interpreted as resistant.

SERIAL TUBE DILUTION METHOD

Procedure.—Stock solutions for penicillin, chlortetracycline, chloramphenicol, and oxytetracycline were prepared by adding 20 ml. brain-heart infusion broth to 20,000 γ or units of each antibiotic.§ One milliliter portions of the diluted solution were transferred with aseptic technique to small sterile vials for freezing and storage.

† The Desi-Disks were manufactured by the National-Bio-Test, Inc., Box 1713, Benson Station, Omaha, Neb. The concentrations of the discs used were as follows: sulfisoxazole (Gantrisin), 1 mg.; sulfamerazine, 1 mg.; sulfadiazine, 1 mg.

‡ References 3 and 4.

§ The Antibiotic Diagnostic Kit was obtained from Chas. Pfizer & Company, Inc., 630 Flushing Ave., Brooklyn 6, N. Y.

When needed the frozen stock solutions of each antibiotic to be tested were thawed at room temperature. Dilutions were prepared in a similar manner for each drug.

Of the stock solution 0.5 ml. was pipetted aseptically into a test tube containing 9.5 ml. of sterile brain-heart infusion broth, resulting in a solution containing 50 γ or units per milliliter.

The solution was further diluted by transferring 2 ml. of the latter solution to a test tube containing 8 ml. of sterile broth. The resultant solution (A) contained 10 γ or units per milliliter.

From solution A the desired antibiotic concentrations of 5, 0.5, and 0.05 γ or units per milliliter were obtained by dilution with sterile brain-heart infusion broth and the diluted broth inoculum.

The inoculum was prepared by inoculating a sterile tube of brain-heart infusion broth from the colonies on blood agar plates. The broth culture was incubated at 37 C. overnight and diluted 1 : 1,000 for use.

A protocol of the amounts of each material used in the final dilutions is given in Table 2.

TABLE 2.—*Protocol of Method Used in Dilution of Antibiotics*

Tube No.	Sterile Broth Diluent Added, Ml.	Antibiotic Added	Broth Inoculum (1:1,000) Added, Ml.	Final Conc. Units or γ/Ml.
1	None	1.0 ml. Sol. A *	1.0	5
2	1.8	0.2 ml. Sol. A †	1.0	0.5
3	0.9	0.1 ml. from Tube 2	1.0	0.05
4	1.0	None	1.0	0 (control)

* Sol. A contained 10 units or γ antibiotic per ml.

† Diluent and antibiotic solution mixed and 0.1 ml. transferred to Tube 3; before broth inoculum was added, 0.9 ml. was discarded from Tube 2.

TABLE 3.—*Inhibition of Growth of 102 Strains of Staphylococci in the Tube Serial Dilution Test**

	Antibiotic Concentration in Units or γ/Ml.		
	0.05	0.5	5
Penicillin	74	98	102
Oxytetracycline	20	36	92
Chloramphenicol	11	19	98
Chlortetracycline	7	15	82

* There was no inhibition of growth in the control tubes.

The series of tubes were incubated overnight at 37 C. and examined the next morning for growth. In determining in vitro sensitivity the lowest antibiotic concentration that prevented growth was considered the minimal inhibiting concentration.[2]

Results of Serial Tube Dilution Method.—The organisms recovered from a total of 102 consecutive patients with pustular acne vulgaris were tested by this method. These organisms are also included in the group of 142 that were tested by the paper disc method. In view of the ineffectiveness of the sulfonamides and dihydrostreptomycin as used in the paper disc method, further testing of these drugs was discontinued. Four antibiotics (penicillin, chlortetracycline, oxytetracycline, and chloramphenicol were used and tested in concentrations of 5, 0.5, and 0.05 γ or units per milliliter.

M. pyogenes var. albus was the only organism grown from the acne pustules of this group. Of these, 86 were hemolytic and 16 were nonhemolytic.

As shown in Table 3, penicillin was the most effective antibiotic used under the conditions of this procedure. Oxytetracycline, chloramphenicol, and chlortetracycline were also effective when their concentrations were sufficiently high. It is known that the results of in vitro tests are not always verified by clinical application; however, Schaub and Foley have indicated the minimum effective in vitro concentration of antibiotics which should be of benefit clinically.[2] They consider an organism susceptible to penicillin if it is sensitive to less than 0.6 unit per milliliter. Comparable figures for streptomycin, chlortetracycline, chloramphenicol, and oxytetracycline are listed similarly as 10, 6, 6, and 6 γ, respectively, per milliliter. In view of these criteria, the majority of the organisms tested in this investigation would appear to be clinically susceptible to the antibiotics used.

The relative effect of each antibiotic varied from one test to the next. This was to be expected, since the various strains of staphylococci vary in their sensitivity to the different antibiotics.

CLINICAL RESULTS

Twenty-four of the patients in this study had previously failed to respond satisfactorily to roentgen therapy and the usual therapeutic modalities employed in the management of acne vulgaris. Following in vitro studies each patient was given the drug which appeared most likely to be effective. Seventeen of these received penicillin, 2 were given chlortetracycline, and 3 were given oxytetracycline. Two other patients first received penicillin and later oxytetracycline. All medication was administered orally. The dosage of penicillin was 100,000 units administered three times daily. Chlortetracycline and oxytetracycline dosages consisted of 250 mg. given three times daily. With improvement the dosages were reduced.

The pustular element of the eruption improved promptly within one to two weeks in 20 of the 24 patients. One additional patient also improved satisfactorily after a change in antibiotic therapy was made. He had failed to respond to penicillin, but when he was subsequently given oxytetracycline his response was satisfactory within seven days. In vitro studies indicated both drugs should have been effective. The remaining three patients did not improve while under therapy. The sensitivity tests on one of these three revealed an organism that was not sensitive to any of the drugs utilized. This patient nevertheless was given oxytetracycline first and subsequently penicillin. As might have been predicted, neither antibiotic proved to be effective.

Each of the 24 patients was followed for three months or longer. Clinically the response of 21 of the 24 patients was satisfactory as long as the antibiotic was taken by the patient. Relapse during this period usually occurred if the drug was discontinued.

It is recognized that this is a small group to take under consideration. On the other hand, it should be emphasized that each had been under treatment for months, receiving the gamut of customarily advocated therapy, and yet pustulation and scarring had continued to occur.

COMMENT

Andrews and others have stressed the beneficial effect of the administration of an antibiotic or one of the sulfonamides upon certain patients with acne.[1] The present report, therefore, is concerned with an attempt to determine which of these agents would be more likely to be effective for a given patient. The initial choice of drug is important, and also possibly the second or third choice may be significant in those cases in which the patient is hypersensitive to the first drug or in which the organism becomes drug-resistant.

The paper disc method is a simple and expedient test of in vitro sensitivity but has been criticized as being rather inaccurate.|| The tube serial dilution method is recognized as probably being more efficient, but it is a more time-consuming laboratory procedure.[2]

An attempt has been made to compare the results of both methods when carried out on identical strains cultured from patients with pustular acne. A standard procedure was adopted in order to prevent errors from variation in the media, size of inoculum, the incubation period of the tests, and the stability of the antibiotics. While it is recognized that in vitro tests may be of little value in solving problems of this type, they must not be assumed to be without any value whatsoever. Becker did not find sensitivity tests helpful in the management of 36 patients with acne.[6] However, it should be pointed out that the antibiotic concentrations used by him varied from those used in the present report. He did feel that the oral antibiotics were beneficial in controlling the pustular element of acne. The need continues to exist for some method to indicate beforehand whether a drug is likely to prove therapeutically successful. The alternative of relying upon trial and error is expensive and time-consuming for the patient.

SUMMARY AND CONCLUSIONS

The organism cultured most often from the pustules of 142 patients with acne vulgaris was hemolytic M. pyogenes var. albus.

By the paper disc method of testing the in vitro sensitivity of the drugs used, penicillin was found to be most effective against the organisms cultured from the patients. Oxytetracycline, chlortetracycline, and chloramphenicol, in that order, were found to be next in effectiveness. Dihydrostreptomycin, sulfisoxazole, sulfadiazine, and sulfamerazine were found to be ineffective by the method used in this experiment.

By the serial tube dilution method penicillin was again found to be the most effective drug used. Oxytetracycline, chlortetracycline, and chloramphenicol were found to be effective, although not as efficient as penicillin in the concentrations used.

Results from the paper disc method and the tube serial dilution method gave comparable results when the same drugs were tested against identical strains of staphylococci.

Twenty-one of the 24 patients with recalcitrant pustular acne vulgaris responded satisfactorily when given drugs indicated by in vitro studies as being effective.

|| References 4 and 5.

The paper disc method of determining bacterial sensitivity to antibiotics appears to deserve additional consideration as a preliminary qualitative guide in the management of patients with unresponsive pustular acne vulgaris.

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ACROKERATOELASTOIDOSIS

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IN THE fall of 1952 I presented a report * on a case of dermatosis of a hitherto unreported type to which I gave the name of acrokeratoelastoidosis.[1] Some months after the first case, I came across another which will be described in this paper.

REPORT OF A CASE

M. V. O., a Brazilian Negro woman, a cook, born at Itabira (Minas Gerais) 21-year-old resident in Belo Horizonte.

Personal and Family Antecedents.—These show no aspects which are of interest in the present case.

History of the Present Disease.—The patient said that about two years ago, she noticed on her legs the first manifestations of her present disease.

General Examination.—Nothing abnormal.

Dermatological Examination.—The pathologic process is localized on the lower two-thirds of the anterior surface of the legs, on the anterior surface of the tibiotarsal points spreading to the upper third of the dorsal surface of the feet, and on the internal part of the left malleolar region. The eruption consists of papuloid, corneal, verruciform, or lichenoid elements partly embedded in the skin, slightly raised, of varying dimensions, translucid yellowish, smooth-surfaced, rounded, oval, or quadrangular, arranged in lines which are more or less parallel in a longitudinal direction. The papuloid elements are of firm consistence. On vitropression the underlying surface is seen to be yellowish brown. On the middle third of the anterior surface of the legs, small diffuse keratosic plaques are visible. The normal quadricular marking of the skin over the front of the tibiotarsal joints is greatly accentuated. There are no subjective symptoms of any kind.

Laboratory Tests.—(*a*) Wassermann and Kahn tests, negative; (*b*) parasitologic examinations of the feces, negative; (*c*) complete hemogram, nothing abnormal; (*d*) glucose in the blood, normal; (*e*) urine, normal.

CLINICAL STUDY

The clinical study of this new entity is based on the symptomatology observed in my two cases. In the first case, there was marked accentuation of the normal cutaneous folds on the dorsal surface of the metacarpophalangeal and interphalangeal joints of both hands and there were small papuloid corneal transparent lesions looking like corneal pearls.

On the thenar regions, the posterior surface of the wrist joints, and the dorsal surface of the first interdigital spaces, there are eruptive patches consisting of papuloids, corneal elements which are round, oval, or polygonal. These are separated by small furrows. Their surface is smooth; they are only slightly raised;

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* Presented at the meeting of the Minas Gerais branch of the Brazilian Society of Dermatology, Sept. 15, 1952, and at the 10th Brazilian Congress of Hygiene, held in Belo Horizonte Oct. 19 to 25, 1953.

their outline is more or less well marked; they are confluent or isolated and measure from 1 to 2 mm. They are yellowish, faintly brilliant, and transparent, and are hard on palpation.

On the sides of the feet, on the heels, and on the malleoli, there are papuloid corneal elements, which are round, oval, or polygonal, separated in places by small furrows. Their surface is smooth or slightly squamous; they are slightly raised, xanthomatoid yellowish in color, and firm on palpation. Their outline may or may not be well defined; they are confluent or isolated, and they measure 2 or 3 mm.

Fig. 1.—Acrokeratoelastoidosis of the right leg. A biopsy was made.

Fig. 2.—Acrokeratoelastoidosis of the left leg, showing the site of the biopsy.

In some of the lesions on the foot, there are crater-like hollows of the size of a pinhead; these correspond to the absence of intrapapillary elevations, as was ascertained histologically. The corneal elements both on the feet and on the hands are more palpable than visible in consequence of their being embedded. The papuloid elements become more visible when the skin over the affected region is stretched.

On vitropression the subjacent yellowish-brown surface is seen. There are no subjective symptoms. In the second case reported, the process was localized on the legs, dorsal surface of the tibiotarsal joints, upper third of the dorsal surface of the feet, and left internal malleolar region.

The clinical symptoms have already been mentioned. The etiology of this dermatosis is not clear. The condition seems to be a nevoid anomaly with marked modification of the elastic fibers and of the collagen.

Fig. 3.—Acrokeratoelastoidosis (van Gieson's stain).

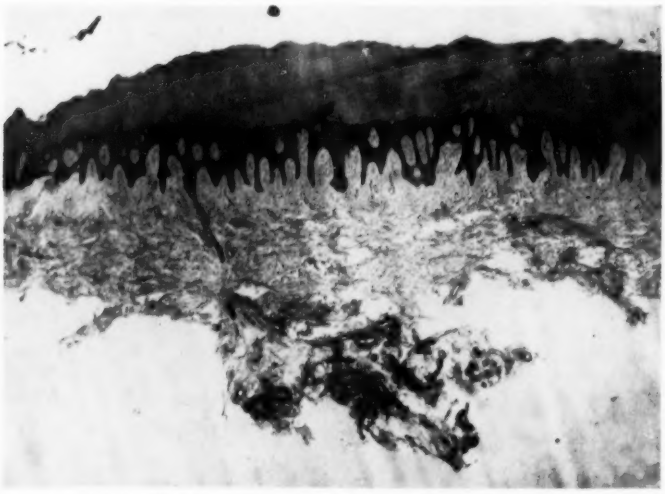

Fig. 4.—Acrokeratoelastoidosis (hematoxylin-eosin-orcein).

DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from colloid millium, pseudoxanthoma elasticum of Darier, juvenile elastoma of Weidman, Anderson, and Ayres, citrine skin of Milian, elastoma of Debreuilh, senile and presenile degeneration, localized

nodular elastoidosis with cysts and blackheads of Favre, nevus of the connective tissue, the chagrin skin of Pringle-Bourneville disease, acrokeratosis verruciformis of Hopf, juvenile verruga plana, epidermodysplasia verruciformis of Lewandowsky and Lutz, hard nevus of Unna, punctate porokeratosis, palmoplantar lichen planus and proteinosis lipoidica.

The pathology of the first case was as follows. A fragment of skin taken from the left thenar region showed that the corneal layer was sinuous and thickened. In the corneal layer there were sudoriparous excretory canals.

The granular layer showed more hyperplasia at the places where there was most thickening of the corneal layer; up to seven or eight rows of cells could be seen. There was slight acanthosis, and in certain places the dermic papillae had disappeared owing to fusion of the interpapillary crests. This fusion corresponded roughly to the thickening of the granular and corneal layers. There were diminution and fragmentation of the elastic fibers. Examination of a fragment of skin taken from the outer surface of the left foot showed that the corneal layer was sinuous and thickened, and sudoriparous canals could be seen. There was hypergranulosis corresponding to the hyperkeratosis. The number of papillae was diminished, owing to fusion of the interpapillary crests. There was dilatation of the blood vessels of the subpapillary layers. There were diminution and fragmentation of the elastic fibers. Metachromatic reaction for mucine was negative. There were no calcareous deposits. There was modification of the collagen fibers.

PATHOLOGY OF SECOND CASE

Fragment of the skin taken from the left foot (Preparation 15043): The corneal layer was sinuous and thickened, and excretory sudoriparous canals were seen. The granular layer was hyperplasic at the level of the areas of hyperkeratosis and up to 10 rows of cells were seen. There was acanthosis, and the number of interpapillary crests was increased. Some interpapillary crests were united. This fusion corresponded to the thickening of the subjacent layers. In the basal layer, there was great diminution of melanin at the thickened areas. In the derma there was papillomatosis and capillary dilatation with hyperplasia of the perithelial cells. The elastic fibers were fewer in number and fragmented. There was homogenization of the collagen of the papillary and subpapillary layers of the derma. There was no modification of the adjacent skin (Figs. 3 and 4). In fragments of skin taken from the right leg (Preparation 15047), the lesions were the same as in Preparation 15043, but were less marked.

SUMMARY

Two cases of a new skin disease are described, to which I have given the name acrokeratoelastoidosis.

Rua Clara, 1991.

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Clinical Notes, New Instruments and Techniques

BULLOUS URTICARIA PIGMENTOSA

Report of An Unusual Case

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DURHAM, N. C.

Bullous lesions in association with urticaria pigmentosa have been observed occasionally since recognition of the disease in 1869. Finnerud,[1] in 1923, in a summary of all reported cases of urticaria pigmentosa found that 8 cases out of a total of 308 had vesicles and bullae. Since 1923, a number of references to bullous lesions in urticaria pigmentosa have appeared in various society transactions. The vesicles and bullae were described as being in association with the usual urticaria pigmentosa. In each case reviewed, the classical lesions of urticaria pigmentosa—macules and nodules—were the outstanding feature, although some lesions were bullous.

The following case presentation is made because of its unusual nature. It represents the only reported bullous eruption having the classical histologic picture of urticaria pigmentosa, without a single macule, papule, or other lesion typical of the disease.

REPORT OF CASE

K. M.—A 6-month-old white girl, was first seen by the pediatric service of Duke Hospital in June, 1953, because of urticarial and vesiculobullous lesions of one and one-half months' duration. Except for irritability and "colic," no other complaints were elicited. The child was born spontaneously at nine months and had had apparently normal development until onset of the present illness. Local physicians had prescribed antihistamines orally and ammoniated mercury ointment locally with little change in the skin disorder. The irritability continued, as did considerable wheal response to scratching and new vesicle formation.

Dermatological consultation revealed that there was marked dermographism present, as well as diffuse patchy erythematous areas and some urticaria-like lesions over the body. In addition, there were a number of vesicles and crusted lesions present over the trunk. Urticaria and impetiginization secondary to intense excoriation, with the possibility of a therapeutic venenata, were considered the most likely diagnoses at the time. The child was placed on a regimen of tripelennamine (Pyribenzamine) elixir ½ tsp. (2 cc.) three times daily and at bed time; and 1% methylrosaniline chloride (gentian violet) in 10% alcohol to the crusted vesiculated areas twice daily. Calamine liniment was prescribed locally, and the parents were advised to avoid all other local medications.

She was seen as an outpatient on two occasions within the next four weeks and presented on the last visit a generalized bullous eruption, the bullae being generally the size of large grapes, containing clear fluid and having no erythema at their base. No mucous membrane lesions were found, and the general health seemed unaffected. Because of the nature of the bullae, pemphigus was considered the most plausible diagnosis.

The child was admitted to Duke Hospital on July 27, 1953. Abnormal physical findings were limited to the skin. The initial laboratory findings were as follows: Hemoglobin was 11 gm., and white blood cells numbered 9,800, with a differential count showing 53% polymorphonuclear cells, 9% stab forms, 35% small lymphocytes, 2% large lymphocytes, and 1% monocytes. Urinalysis revealed an acid pH, no protein, and no sugar; microscopic examination was normal. Stool examination failed to reveal any abnormality. Repeated bacterial cultures of blister fluid revealed

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Fig. 1.—Close-up of abdomen, demonstrating linear nature of the bullae. The darkened areas are due to presence of methylrosaniline chloride (gentian violet).

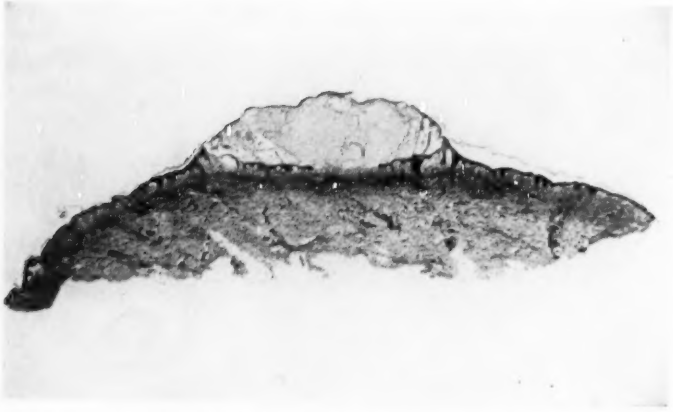

Fig. 2.—Intraepidermal bulla and dense subepidermal infiltrate of mast cells. × 10.3.

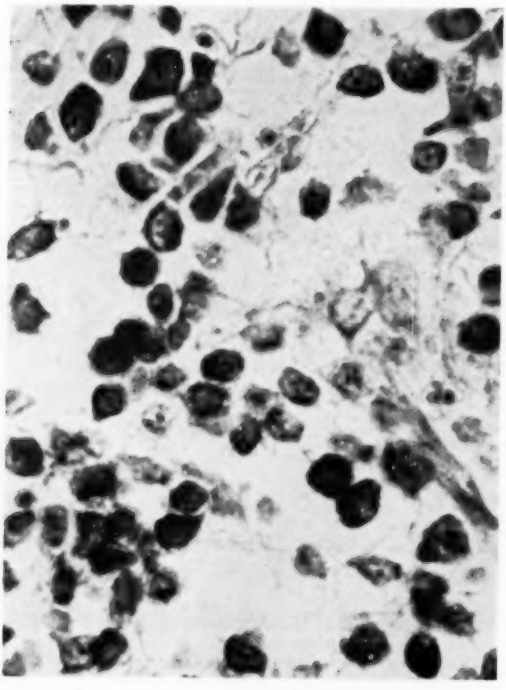

Fig. 3.—Photomicrograph of subepidermal infiltrate, showing presence of cuboidal mast cells. × 957.

no significant organisms, although Micrococcus (Staphylococcus) aureus and M. albus were found in several old lesions that had become pustular. Tzanck tests performed on blister fluid failed to establish a specific diagnosis.

An intact, fresh bulla was removed on the day of admission. The histologic findings were those of an intraepidermal bulla, with a thick band-like infiltrate subepidermally, consisting of masses of cuboidal cells which, on Giemsa stain, showed the characteristic appearance of mast cells. These findings were confirmed by Dr. Herman Beerman, of Philadelphia.

Course in Hospital.—New bullae continued to shower after admission, despite dietary management, sedation, and other supportive measures. Corticotropin (ACTH) gel therapy was instituted, the child receiving 30 units twice daily initially and for a total of two days. The dosage was then dropped to 20 units twice daily for one day, and then 10 units twice daily. No new lesions were observed after use of corticotropin was instituted, and, with marked clearing of the impetiginized areas, she was discharged with instructions that she receive corticotropin gel, 10 units every other day, and diphenhydramine (Benadryl) hydrochloride elixir, ½ teaspoon every four hours.

The child continues to do well after discharge from the hospital. The dosage of corticotropin gel was lowered to a single weekly injection of 10 units. She continues to manifest mild urticarial lesions but no new bullae have appeared. Two months after leaving the hospital, the child appears to be in good health, with no cutaneous lesions.

COMMENT

There seems little doubt as to the classification of this bullous eruption. The presence of Darier's sign and the histologic findings established urticaria pigmentosa sans pigmentation.

The decision to employ corticotropin was reached only after an extensive and an all-inclusive conservative therapeutic regimen. The response was quite dramatic, and therefore prompts the suggestion that the steroids may be used in other cases of urticaria pigmentosa to control acute exacerbations of the disease.

SUMMARY

A peculiar bullous eruption in an infant has been described. The histologic diagnosis of urticaria pigmentosa was established, and a brief review of the literature included.

The successful use of corticotropin gel in urticaria pigmentosa is reported.

REFERENCE

1. Finnerud, C. W.: Urticaria Pigmentosa (Nodular Type) with a Summary of the Literature, Arch. Dermat. & Syph. **8**:344, 1923.

TREATMENT OF ALOPECIA AREATA WITH AMMOIDIN-AMMIDIN SOLUTION

Preliminary Report

LEONARD E. SAVITT, M.D.
LOS ANGELES

A solution consisting of 7.5 mg. of ammoidin and 3.75 mg. of ammidin per milliliter in isopropyl alcohol,* recently used for the treatment of vitiligo, was used on patients with alopecia areata in an attempt to cause regrowth of hair by the production of erythema or other mechanisms.

Subjects consisted of three patients with multiple patches of alopecia areata, who were otherwise normal. Some of the areas of alopecia areata of each patient were treated by light application of the aforementioned liquid once each week and, as controls, other areas in each patient

* Biomoidin Liquid (Bioproducts Oregon, Ltd., Warrenton, Ore.)

were treated with concentrated phenol, followed by neutralization with isopropyl alcohol. All areas were irradiated with cold quartz light (wave length—2,537 A.) at 1 in. (2.5 cm.) distance, starting with 15 seconds and increasing 15 seconds at each subsequent treatment, at each visit. In addition, an intramuscular injection consisting of 10 mg. of folic acid, 60 γ of vitamin B_{12} in crude liver, U. S. P., 10 γ (from 10 γ per milliliter) was administered weekly.

Response to treatment was observed and charted over a period of six months. The patients did not know that an experimental solution was being used, or on which areas; however, in several instances, patients remarked that certain of the treated areas became "sore" (those that I knew were treated with phenol), while other areas did not.

In a 22-year-old woman, the regrowth of hair in the areas treated with ammoidin-ammidin liquid was distinctly more rapid than that in the areas treated by phenol followed by alcohol. In a 24-year-old man, the hair of the areas treated with each preparation regrew at approximately the same rate. In a 27-year-old woman, hair regrew readily in areas treated with ammoidin-ammidin solution, while areas treated with phenol-alcohol failed to regrow for a period of two months. When ammoidin-ammidin solution was applied to those areas previously treated by phenol-alcohol, regrowth of hair occurred readily and completely.

CONCLUSION

From preliminary observation of treatment of alopecia areata in three patients, it is my impression that application of an ammoidin-ammidin solution causes regrowth of hair more rapidly than the commonly used phenol-alcohol solution, without even the mild discomfort to the patient produced by the latter preparation. However, it will be necessary to observe the results of treatment of many more patients with this preparation before final conclusions can be reached.

ADDENDUM

Since this article was written, my attention has been called by other dermatologists to several instances of severe vesiculation in patients with vitiligo treated by the aforementioned solution. However, each patient with alopecia areata is warned by the author to avoid exposure to sunlight over 15 minutes and thus has had no instances of more than moderate erythema.

1033 Gayley Ave.

Society Transactions

LOS ANGELES DERMATOLOGICAL SOCIETY

J. Walter Wilson, M.D., President

Anker K. Jensen, M.D., Secretary

Jan. 12, 1954

Chronic Porphyria (Porphyria Hepatica, Mixed or "Cutana Tarda" Type). Presented by DR. M. E. OBERMAYER and (by invitation) by DR. M. C. ZIMMERMAN.

A 52-year-old house painter was in good health until 1933, when he developed a peculiar dark-gray tan on sun-exposed areas. This continued until 1947, when blisters and crusting occurred that caused pitted scars on healing. About two hours after he was painting on the sunny side of a house, itching and burning occurred on the exposed parts of the body. The hands developed some painless blisters following exposure to paint thinner. The above symtoms stopped from 1936 to 1945, while he was employed as a custodian and worked inside. During these years exposure to the sun (while fishing) had no significant effect. Symptoms began again in 1946, when he returned to painting.

About 1951, he noticed that if he retained his urine for a long time it was reddish in color and that it turned a dark red if kept in a container for 24 hours. He gives no history of taking drugs but admits a moderate amount of drinking. He has had scarlet fever, pneumonia, and gonorrhea. He states he has not had gastrointestinal symptoms, except for an acute attack of gastrointestinal colic in 1929, which he ascribed to painter's colic. During childhood his legs were severely burned with kerosene, and the scar on the right posterior thigh broke down about one year ago and has been ulcerated ever since. No other member of the family has had skin trouble, photosensitivity, or discolored urine.

The skin on the face, neck, chest, and shoulders exhibits a distinctive grayish pigmentation and a slightly glazed appearance. There are also many hyperpigmented and depigmented scars on the face, neck, and scalp, and some tense bullae on the hands. There is also an ulcer on the posterior surface of each thigh in the old atrophic scar tissue.

The blood showed a 4+ Kahn reaction, and two repeat Treponema pallidum immobilization tests were invalid. There was no sugar or albumin in the urine. The urine fluoresces bright pink with Wood's light also when acidified. After the removal of coproporphyrin with acidification and washing with ether, the fluorescence still persists, showing the presence of uroporphyrin. Nov. 18, 1953, the total porphyrins in a 24-hour specimen were 11,000 mg. coproporphyrin and 15,600 mg. uroporphyrin. On Dec. 2, the total porphyrins were coproporphyrin 1,470 mg. and uroporphyrin 12,830 mg. On heating, urobilinogen concentration diminished from 12.8 to 10.67 mg., thus excluding the presence of porphobilinogen as this increases on heating.

Normal erythema developed after exposure to light waves of 2,537 and 2,967 A. and also to a mixture of both. No erythema developed after exposure to 3,660 A. or to wave lengths shorter than 3,166 A. The patient's serum was injected into the arm of one of us (M. Z.), and no evidence of photosensitivity developed at the site of injection after exposure to wave lengths of 2,500, 2,900 or 3,600 A.

The blood count was within normal limits, as were the liver function tests. The biopsy specimen was consistent with a sun-sensitive dermatitis. The patient's general physical condition has not changed after injections of penicillin, crude liver, vitamin B complex, and other supportive therapy.

DISCUSSION

DR. L. H. WINER: I suggest the diagnosis of epidermolysis bullosa of the hyperplastic type. A section from the thigh stained with hematoxylin and eosin showed subepidermal blisters covered by atrophic epidermis. The connective tissue of the cutis formed the floor of the blister. Two other histologic preparations showed the cutis entirely replaced by heavy fibrous connec-

tive tissue as is seen in a keloid. Keloids and hypertrophic scars are seen in the hyperplastic dystrophic type of epidermolysis bullosa. I would suggest an elastic stain on the histologic sections. If the skin is deficient in elastic, it would lend support to the diagnosis of epidermolysis bullosa. Clinically, except for the hands, blisters on the covered portions of the body are suggestive of epidermolysis bullosa, whereas in porphyria, blisters favor the exposed surfaces.

DR. SAMUEL AYRES, JR.: It is my understanding that the acquired type of epidermolysis bullosa may show porphyrin and that the lesions can be produced either by trauma or light sensitivity or both and may be associated with liver damage. This man has been a painter for years; maybe he has poisoning from lead. He apparently has syphilis, judging from his serology. I think it is an acquired type of epidermolysis bullosa plus porphyria due to toxic injury.

DR. HAROLD PRICE: Regarding the development of blisters, the patient stated definitely that he did not develop them following trauma, but he did say that his skin was tender and if he scratched himself it would peel off easily. My concept of epidermolysis bullosa is that a bleb will develop at the point of trauma. What he describes sounds more like a Nikolsky sign.

DR. MURRAY ZIMMERMAN (by invitation): In reply to Dr. Winer, epidermolysis bullosa, by definition, is a disease characterized by formation of blisters in response to trauma and hence on palms and soles. This patient has blisters on light-exposed areas only, none on the palms and soles, and one after trauma. Secondly, while true epidermolysis bullosa may be associated with an increased excretion of porphyrins, so may many other diseases, and that is not a significant differential. An extremely high excretion of uroporphyrin makes the diagnosis of porphyria. As soon as fluorescence is seen in urine which has been acidified with hydrochloric acid, porphyrinuria is diagnosed; with glacial acetic acid saturated by that extraction, if there is a fluorescence in the aqueous, a diagnosis of porphyria is made right then, since this is uroporphyrin. Elastic tissue stains were not done in this case but will be. It is of interest that in the slides in light-exposed areas no elastic tissue degeneration or other evidence of sunlight damage was shown. The improvement and healing of the patient's ulcers has been trebled in speed with ultraviolet (Kromayer) therapy in heavy doses. His light sensitivity is not to these wave lengths. His skin picture is so characteristic of previous descriptions of this type of prophyria that he has been presented as a classic example rather than as a diagnostic problem. Liver function tests are at the borderline of normal. Further liver function tests would not establish more information or change his diagnosis or treatment. Before I saw him, he had had penicillin for other diseases, which had no effect on the lesions. Since I first saw him he has had 9,600,000 units of penicillin. Whether or not he has syphilis, I do not know. Two Treponema pallidum immobilization tests have been invalid in his case. I have talked with Dr. Watson about this and he ran the levels. The definition of porphyria I quoted was that of Brunsting and Mason. Watson is considered the outstanding authority on porphyria in the United States. Porphyria is an inborn error of metabolism which alcoholism may exacerbate and change from a latent to a clinical form, just as obesity may do for diabetes. It is true that experimental porphyria has been produced in animals ever since 1895. Rabbits and rats treated with Sedormid (allyl-isopropyl-acetyl-carbamide) show a marked drop in liver catalase activity, and a concomitant rise in liver porphyrins is apparently due to a blocking of porphyrin utilization for catalase synthesis. Like alloxan diabetes, this is a laboratory animal procedure only. Human porphyria, like human diabetes, is different.

Micropapular Tuberculid. Presented by DR. A. FLETCHER HALL.

Mrs. K. M., a married woman, aged 34, had an eruption on her chin similar to the present one about a year ago. This responded to x-ray treatment and calcium injections. The present attack appeared suddenly several months ago. There is no itching and relatively little erythema on awakening, but these symptoms become more prominent during the day.

Both sides of the chin present a poorly limited, silver-dollar-sized patch of pale pink, fine, firm papules, some of which are domed while others are sessile. Diascopy reveals fine, pinkish-brown points.

The Mantoux test was positive in dilution 1:10. Microscopic examination revealed an atrophic epidermis. Directly underneath the atrophic epidermis in the cutis is a nodular mass of epithelioid cells with a slight round cell infiltrate and no evidence of necrosis. There is an occasional giant cell seen in some of the sections.

DR. NELSON PAUL ANDERSON: I would suggest the diagnosis of so-called micropapular tuberculid of Michelson and Laymon. I have never seen such small lesions in lupus disseminatus faceii. I have observed the latter condition only in Negroes, and there was practically always involvement of the nasolabial folds. A positive tuberculin test would suggest that it does not belong in the sarcoid group.

DR. L. H. WINER: Clinically, the lesions in this patient are smaller than those seen in lupus miliaris disseminatus faceii. Histologically, the sections do not show central caseation necrosis but rather resemble a sarcoid in structure, having epithelioid cell tubercles. Patients with lupus miliaris disseminatus faceii and sarcoid frequently show negative tuberculin reactions. The positive tuberculin test, together with clinical and histopathological findings, would confirm the diagnosis of micropapular tuberculid.

DR. SAMUEL AYRES III: I agree it is probably some form of tuberculosis. As far as therapy goes, I would suggest isonicotonic acid hydrazide, but combined with streptomycin or paraaminosalicylic acid (PAS), as bacterial resistance develops much more slowly with this combination.

DR. BEN A. NEWMAN: I would request an x-ray of the chest.

DR. A. FLETCHER HALL: I have withheld nicotinic acid hydrazide compounds until I could show the case, because I have heard of similar dermatoses disappearing promptly under such therapy. The sudden appearance made me think of neurodermatitis at first. If any girl has a right to have neurodermatitis, this one has. When she had been married only five months, her husband was in an automobile accident and is now a paraplegic and has been moved from hospital to hospital. The first attack of her dermatitis occurred shortly after the accident, and the second occurred just before his transfer to a veteran's hospital in the West; the sudden onset of both attacks and the clearing of the first one, after treatment by Dr. Guy in Pittsburgh for neurodermatitis, suggested that diagnosis, and I did not awaken to the true diagnosis for several weeks.

Porokeratosis (Mibelli) in Two Siblings. Presented by DR. NELSON PAUL ANDERSON and (by invitation) DR. ERNEST THOMAS FOX.

Case for Diagnosis: Chronic Aphthous Ulceration with Secondary Verrucous Structure. Presented by DR. MOLLEURUS COUPERUS and (by invitation) DR. ERNEST THOMAS FOX.

Case for Diagnosis: Nail Defect of Thumb. Onychogryphosis? Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III.

Lymphoblastoma (? Type). Presented by DR. NELSON PAUL ANDERSON and (by invitation) DR. LYON ROWE.

Chronic Exudative, Lichenoid and Discoid Dermatitis of Sulzberger and Garbe. Presented by DR. HAROLD PRICE.

Alopecia Totalis. Presented by DR. STANLEY C. ANDERSON and (by invitation) DR. VINCENT P. BURBY.

Ocular Pemphigus. Presented by DR. VICTOR D. NEWCOMER and (by invitation) DR. R. H. ZEILENGA.

Nevus (Junction Type). Presented by DR. SAMUEL AYRES JR. and DR SAMUEL AYRES III.

Acne Vulgaris in a Young Child. Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III.

MANHATTAN DERMATOLOGICAL SOCIETY

Jack Wolf, M.D., President

George M. Lewis, M.D., Secretary

Oct. 13, 1953

Prurigo Mitis Occurring in Five Members of a Family. Presented by DR. MAURICE J. COSTELLO.

C. R., a woman aged 39, a daughter aged 17, a daughter aged 7, a son aged 8, and a daughter aged 5 years came to the United States from Puerto Rico in May, 1953. One month later they developed papular urticarial lesions on the extensor aspects of the extremities. Because several members of the family were similarly affected by a pruritic dermatosis, scabies was considered, but this diagnosis was discarded on clinical grounds. We have observed the occurrence of several members of Puerto Rican families simultaneously affected by prurigo mitis. This is unique in our experience. We have never observed this in nationalities other than Puerto Ricans. Change of climate and high-carbohydrate, low-protein diets probably explain the condition. However, the mother stated that the diet here is as good as (if not better than) the one they had in Puerto Rico. The patient claims she has seen sand flies in her apartment.

DISCUSSION

DR. ORLANDO CANIZARES: I asked about the bugs in the home, and they have all kinds of bedbugs, cockroaches, etc. I am inclined to agree with Goldman that some of these cases may be classified as urticaria due to insect bites. On my recent trip to Cuba, I saw many cases, and Pardo-Castello said there are many cases on a nutritional basis and due to intestinal parasites, and that when the underlying condition is treated the patients get better.

DR. FRANK C. COMBES: I agree with the diagnosis of prurigo mitis. It is certainly unusual to see so many cases in one family, but when one thinks of the possible pathogenesis of a condition such as this one may wonder why it has not been seen before. Entire families migrate to a new location and take up a different diet. Erythema multiforme, which in many cases is based on intestinal intoxication, is seen in immigrants. Certainly, I think a change in diet may contribute to it. I have never seen it in a family involving both adults and children, so there is probably much in what Dr. Canizares says regarding intestinal parasites. Growth of the parasites may be fostered or enhanced by some change in diet. I doubt that there could be any animal parasite without some hematologic changes, such as eosinophilia. I agree that it is chronic papular urticaria or prurigo mitis.

DR. SAMUEL M. PECK: According to Dr. Costello's history, the father did not manifest any bites. This, I believe, speaks against an infestation with scabies or perhaps fleas. However, during my tour of duty in Washington, I studied the results of rat flea bites among stenographers in old government buildings. It was obvious that not all the girls were affected because the fleas seemed to have a predilection for certain people. I believe in this instance one leg of one of the patients should be protected with an insect repellent to see if the question of insect bites can be ruled out.

DR. JACK WOLF: We have had occasion to study this type of reaction in families and I am inclined to take the mother's history literally. They have bedbugs, and an exterminator should do a good job. The conditions under which these people live are terrible.

DR. PERRY SACHS: The fact that the onset of all the cases was at the same time suggests external parasites as the causative factor, in contrast to intestinal parasites or other causes.

DR. WILBERT SACHS: It was my first impression that prurigo mitis does not develop suddenly. The lesions are too sparse. On the other hand, there are features against scabies and external parasites. Should the condition not respond to treatment for external parasites, it may well belong to the group Dr. Costello mentions, but I would like to see a section, for one would get an entirely different picture in the different conditions.

DR. DAVID BLOOM: I favor the diagnosis of papular urticaria, most probably due to external parasites. The fact that all members of the family are affected speaks against the diagnosis of prurigo mitis, which, I believe, is related to atopic dermatitis which is hereditary.

DR. MAURICE J. COSTELLO: This isn't the first group of cases of this type we have seen. There have been at least six Puerto Rican families in which five or six members were affected in a similar manner. The point Dr. Canizares brought out in regard to intestinal parasites is interesting, but I would agree with Dr. Combes that these people frequently develop urticaria after they come to the United States. Parasitic infestation would not be confined to the extensor surfaces, but would affect all parts. I rarely see prurigo mitis in the well-to-do or private patients, but it is common in clinic and municipal hospital patients in this city. I still believe these patients have prurigo mitis and that the causes are change of climate and a high-carbohydrate, low-protein diet. The father in these families is rarely affected. He often precedes his family's arrival by six or seven months. The lesions eventually clear up. Within a year the eruption disappears, and even though they live in the same house it does not persist.

Acrodermatitis Enteropathica. Presented by DR. DAVID BLOOM.

N. M., a boy aged 4 years, born in Italy, and in the United States for one month, was seen for the first time at the New York Skin and Cancer Unit on June 5, 1953. At that time he presented fairly well-defined, erythematovesicular, scaly plaques over the Achilles tendons, the sides of the heels, the plantar surface of the toes, in the popliteal spaces, on the knees and

elbows, arms and forearms, in the intergluteal fold and adjacent areas of the buttocks, and on the distal part of the penis. Satellite vesiculopustules were also present on the feet. The angles of the mouth and the edges of the eyelids showed erythema and slight crusting. All the fingernails and toenails were brownish-discolored, thickened and distorted, and associated with severe paronychia. The buccal mucosa showed reddish and whitish spots, and the tongue was covered with a white fur. The entire scalp was covered with thin, fuzzy hair, and the eyebrows were thin, particularly in the lateral aspects.

The parents stated that the boy was born at full term, delivered by a midwife. Two days later, convulsions developed which were considered due to intrapartum cerebral hemorrhage. These convulsions never recurred. At the age of 3 months, perianal and intergluteal erythema appeared which lasted for about three months and reappeared several months later. At the age of one year, after the patient had whooping cough and measles, the eruption became worse and gradually involved other skin areas and the nails. The hair on the scalp, which was present at birth as fuzz and which had grown a little only in the vertex and occipital areas, fell out at the end of a year and since then has consisted of thin fuzz over the entire scalp.

At the age of 6 months, the child had diarrhea periodically every four to eight weeks, with four or five bowel movements associated with abdominal discomfort, anorexia, and apathy. These attacks were associated with exacerbation of the eruption. The tongue became coated, and pronounced halitosis was present.

The parents are first cousins through the maternal side. A younger sister, aged 2 years, is perfectly well. No other member of the family is affected.

During exacerbations since the child has been under observation, the erythematovesiculobullous eruption on the feet became so severe that the patient had great difficulty in walking. His sad appearance and apathy during attacks changed to cheerfulness during remission, at which time the plaques became drier and appeared hyperkeratotic and exfoliating.

Blood cell counts were normal, except for a relative lymphocytosis of 48%. The erythrocyte sedimentation rate was increased to 42 mm. Roentgenograms of the chest and gastrointestinal tract showed no abnormality.

Mycologic examination revealed Candida albicans at the angles of the mouth, in a pustule on the foot, and in the nails, but the other cutaneous lesions and the tongue yielded no Monilia. In one pustule, in addition to C. albicans, many colonies of Staphylococcus aureus, coagulase-positive, and nonhemolytic streptococci were found on subculture.

Blood chemistry examinations, including calcium, phosphorus, nonprotein nitrogen, and albumin and globulin, gave normal results. On one occasion the fasting blood sugar was 30 mg. per 100 cc., on another 60 mg. per 100 cc., and the sugar tolerance curve was normal. Intradermal test with oidiomycin was positive at 1 : 1,000 but negative at 1 : 10,000.

The feces showed frequent fat globules. The culture was negative for pathogens. Cysts of Giardia lamblia were found.

Biopsy from a lesion on the hand showed intraepidermal vesicles with marked inflammatory reaction of the papillary bodies. The upper cutis showed an infiltration of round cells and wandering connective tissue cells.

Biopsy from a plaque on the leg showed the epidermis irregularly acanthotic, with an increased granular layer and diffuse, thin keratosis. In the cutis, the blood vessels were enlarged and filled with erythrocytes, their walls not thickened. The upper cutis showed a mild cellular infiltration consisting of round cells and wandering connective tissue cells.

Treatment, which consisted first of application of antibiotic ointment and potassium permanganate baths, was of some benefit. But only since the administration of diiodohydroxyquinoline (Diodoquine), which was given first in the dosage of 210 mg. twice a day, was definite improvement noted. In addition, methylpararosaniline chloride (gentian violet), 2% in alcoholic solution, was applied to the lesions. It was found necessary to increase the dosage of the drug to three times a day, and soon afterwards to four times a day. Iodochlorhydroxyquin (Vioform) cream was then substituted.

During the past month, the eruption has almost disappeared, and only dry, mildly red, erythematous plaques were left. The attacks of diarrhea have also ceased. The hair on the scalp also seems stronger.

DISCUSSION

DR. FRANK C. COMBES: The presentation of this case is certainly unique, I think, in dermatologic societies. It throws a question mark on our diagnosis of epidermolysis bullosa, particularly that of the simple type. Most of you are acquainted with those cases reported in the literature previously by Danbolt and recently in this country (Dillaha, C. J.; Lorincz, A. L., and Aavik, O. R.: Acrodermatitis Enteropathica, *J. A. M. A.* **152**:509 [June 6] 1953). Candida albicans has been demonstrated in the bullous eruption. These patients responded very well to the administration of diiodohydroxyquinoline. I think we must reevaluate our interpretation of some of these cases of epidermolysis bullosa. I am going to write to my patients and have them come in and have smear tests for C. albicans.

DR. SAMUEL M. PECK: Many years ago in conducting a children's allergy clinic in the Mount Sinai Hospital, I often made a diagnosis of eczema, even including that of the atopic type which later manifests itself as true psoriasis. Psoriasis in children is often eczematoid and is difficult to recognize. It struck me at that time that it was fairly easy to culture C. albicans both from the stools and from the skin lesions in children with psoriasis.

DR. PERRY SACHS: I looked at both slides, and neither showed any evidence of psoriasis. One shows a bullous reaction, which is intraepidermic, and this finding would be against the diagnosis of epidermolysis bullosa.

DR. WILBERT SACHS: In spite of the article, I have never seen bullous psoriasis. This patient struck me as so much like two brothers with moniliasis whom I treated, that in spite of the negative examination I would like a further search made for Monilia.

DR. NATHAN SOBEL: I have observed the child for several months and there has really been a remarkable improvement, beginning right after diiodohydroxyquinoline was started. The only case in which it has been reported as being used before was that of Rothman and Dillaha. Response came within a few days, as with this child. Besides the cutaneous lesions there is universal alopecia and also intestinal symptoms. Diiodohydroxyquinoline was tried in the Chicago case because it has some action against amebiasis. Someone proposed that the whole syndrome may be due to intestinal infection. These cases also at times run in families, although very few have been reported.

DR. MAURICE J. COSTELLO: I would like to ask whether C. albicans is considered causative in this case, since that organism is physiologically present in the intestinal and respiratory tracts.

DR. DAVID BLOOM: I am inclined to consider the possibility that acrodermatitis enteropathica is related to epidermolysis bullosa. Several cases in the literature (including those of Guy and Wende, for instance, which have great resemblance to these cases) have been reported as atypical epidermolysis bullosa and have features which strongly suggest that diagnosis. Close observation of patients with epidermolysis bullosa, particularly of the dystrophic type, forces one to accept the theory that epidermolysis bullosa is a hereditary metabolic disturbance. So also acrodermatitis enteropathica must be considered as a hereditary metabolic disturbance leading to dysfunction of the gastrointestinal tract, with resultant skin changes and alopecia. To the seven familial cases in the literature must be added mine, in which there is consanguinity of the parents. The finding of Monilia in one of the pustules on the skin, in the nails and in the perlèche lesion is, I believe, due to secondary infection and is not to be considered as primary moniliasis. The location of bullae intraepidermally does not weigh at all against the diagnosis of epidermolysis bullosa. The dramatic effect of diiodohydroxyquinoline, which acts mainly on the gastrointestinal tract and is only slightly absorbed, is still obscure.

Malignant Melanoma of Eleven Years' Duration. Presented by DR. MAURICE J. COSTELLO.

C. C., a woman aged 78, was previously presented before the New York Dermatological Society on Nov. 27, 1951, with the history that nine years before that she had noticed a small dark spot on her right cheeck which gradually increased in size. About six years later the center of the pigmented area became scaly and formed a crust which, when accidentally rubbed off, left a small ulcer. A jet-black, horny excrescence formed on this which measured ¾ by ½ in. (1.9 cm. by 1.2 cm.) at the time it was removed for biopsy. The base was purulent and

vascular. The solid black pigment about the margin of the protuberance became lighter peripherally. The borders of the surrounding rectangular patch measured 2¼ by 1¼ in. (5.7 by 3.1 cm.), and the pigment was distributed in a reticulated, less intense manner.

The biopsy report of Dr. Fred D. Weidman stated that a melanoma of the utmost malignancy was exhibited. At one or two places the epidermis was still present, more or less ulcerated. There was no evidence of a preceding dermoepidermal nevus; in fact, the tumor cells appeared to be continuous with the epidermal ones, and accordingly there might be some justification for designating this lesion as a melanocarcinoma. In any event, the tumor consisted of cells which were solidly packed and distributed diffusely, without any alveolar patterning. If there was any patterning at all, it was in the form of interlacing, vaguely indicated bundles. The tumor cells were for the most part undifferentiated polygonal or spindle forms, which could be those of either an anaplastic squamous cell cancer or malignant melanoma. Certain cells, however, had a rarefied cytoplasm and others contained goodly quantities of pigment, but these were comparatively rare. The nuclei were of the usual large and hyperchromatic kind which characterize malignant growth. Mitotic figures were relatively uncommon but by no means difficult to identify.

A roentgenographic examination of the chest taken Dec. 7, 1951, revealed "four fairly well circumscribed round and ovoid densities in the right lung field, entirely consistent with metastases." Reexamination of the chest on July 9, 1953, again revealed nodular circumscribed densities in the right mid-lung field interpreted as parenchymal metastases.

The patient has developed slight elevation and keratosis of a pea-sized area in the upper margin of the lesion. The patient's health has improved since she was last presented. She has gained 10 lb. (4.5 kg.).

DISCUSSION

DR. NATHAN SOBEL: It is very interesting that this patient has such a malignant melanoma and yet survives. As Dr. Costello said, it has nothing to do with treatment, as there has been no treatment, with excellent results so far. I have a faint recollection that there have been some other cases of melanoma and other malignant lesions (very rare) that heal spontaneously, and the patient seems to develop an immunity. Another point is that when you remove a melanoma, metastases may not take place for many years. This patient has developed some sort of immunity.

DR. FRANK C. COMBES: It is fortunate that the patient did not have radical surgery performed.

DR. WILBERT SACHS: From the way the case was presented, the pathology, and the history one can hardly doubt the diagnosis, and yet it is difficult to believe the story. I certainly would not suggest doing anything, but I would like to have a biopsy section of that brown spot, because the pigment is not uniform. Dr. Weidman speaks of anaplastic epithelioma and that it is highly malignant. That may be so, but Bowen's tumor can give you that picture and last a long time.

DR. PERRY SACHS: On the basis of the microscopic description, I accept the diagnosis. However, I saw a similar lesion recently on the back. As in this case the center was clear, the periphery showed pigmentation, and the lesion had an atrophic appearance. Microscopically, the lesion proved to be a pigmented basal cell epithelioma.

DR. SAMUEL M. PECK: I accept Dr. Costello's diagnosis. However, in my opinion, radical surgery is being performed too frequently when a diagnosis of melanocarcinoma is made. The pathological diagnosis of melanocarcinoma without the evaluation of the lesion itself is not an indication for radical surgery. I base this on follow-up examinations in some of my cases with proved melanocarcinoma, in which a more conservative surgical procedure was carried out.

DR. MAURICE J. COSTELLO: The tendency is toward conservative treatment today. I have at least six cases, some of which I have presented to this society through the years with a diagnosis of melanocarcinoma, made not by one good pathologist but by two or three. These patients are alive and well, one for 12 years. In this case, Dr. Weidman says "this is a

melanocarcinoma of the utmost malignancy," with metastases. I am inclined to think she has melanocarcinoma with metastases, and is doing well under these paradoxical circumstances.

DR. THOMAS N. GRAHAM: I wonder whether the patient's age has anything to do with the slowness of the process.

Case for Diagnosis (Pustular Psoriasis, Resistant to Therapy?) Presented by DR. MAURICE J. COSTELLO.

A. B., a woman aged 40, was previously presented at a meeting of this society where the consensus was that she had pustular psoriasis confined to her palms and soles. At that time she had had the eruption for more than two years, and because of its recalcitrance to therapy she was hospitalized, and responded well to corticotropin (ACTH) and cortisone therapy. The eruption had almost disappeared on discharge. When she returned to work, the eruption reappeared worse than before. The eczematoid pustular psoriasis spread to include the feet and ankles, lower third of the legs, the inner aspects of the thighs, the hands, and posterior elbow regions. From that time to the present, she has received occasional doses of roentgen rays, potassium permanganate, Alibour solution (solution containing zinc and copper sulfates), boric acid, and aluminum acetate solution (Burow's solution) compresses, and most of the common antibiotic ointments, including oxytetracycline (Terramycin), bacitracin, chlortetracycline (Aureomycin), erythromycin, neomycin; hydrocortisone acetate (Hydrocortone) ointment 1% and 2.5% were applied locally. Corticotropin (Acthar gel) and cortisone were administered over a relatively long period. Cortisone apparently made the eruption worse. However, it has been kept under control, and the exacerbations have been improved by the intramuscular injections of 40 units of corticotropin (Acthar gel) two or three times weekly. Internal medical treatment has also consisted of chlortetracycline (Aureomycin), streptomycin, erythromycin and oxytetracycline (Terramycin) at regular intervals, with indifferent results. Sulfapyridine and quinacrine (Atabrine), the latter suggested by Dr. Cormia when the patient was seen at a meeting of the New York Dermatological Society, have been of no avail. The most effective local therapy has been compresses of silver nitrate, 1:1000. She has recently received injections of 1,000 mg. of vitamin B_{12}.

Blood cell counts have been within normal limits and urinalyses have been normal.

DISCUSSION

DR. SAMUEL M. PECK: Antimony tartrate has been used intravenously as a therapeutic agent in pustular psoriasis; it does not work well in ordinary psoriatic lesions. In any type of psoriasis, especially the eczematoid variety, the patient may have a tendency to a Koebner phenomenon, and in such patients, local treatment should be of the blandest type. I give intramuscular injections of vitamin A in spreading psoriasis, about once a week. In the presence of a Koebner phenomenon, about four injections are required to obtain a negative Koebner test. At that point it is safer to use strong antipsoriatic measures.

DR. MAURICE J. COSTELLO: What is the rationale?

DR. SAMUEL M. PECK: I have no rationale; the use of vitamin A is based on observations made in patients with psoriasis when I was studying blood levels of vitamin A following its injection intramuscularly as a control measure in my study of Darier's disease. I noticed this clinical response in a certain number of patients with psoriasis.

DR. WILBERT SACHS: If this patient has what you call pustular psoriasis, then the rest of the eruption has nothing to do with it. If the rest of the eruption does have something to do with it, then it is not psoriasis. I do not know what the patient has, but would like to see a biopsy specimen of one of those vesicles. In true pustular psoriasis one gets pustules wherever the eruption is, not just on the palms and soles.

DR. DAVID BLOOM: At present I cannot find any features favoring the diagnosis of pustular psoriasis. Some years ago I thought pustular psoriasis to be incurable, but I later found that these cases respond to treatment with crude coal tar or in conjunction with ultraviolet light.

DR. MILTON REISCH (by invitation): There is no dermatitis of the backs of the toes, which would be somewhat against stockings, toecaps, and short socks as causative agents.

DR. MAURICE J. COSTELLO: Certainly the picture tonight is entirely different than it was originally. At that time there were two fairly well-demarcated patches which worsened after treatment.

Atopic Cheilitis. Presented by DR. FRANK C. COMBES.

G. W., a woman aged 27, first developed cheilitis eight years ago, which cleared in three weeks. Patch tests with her lipstick at that time were negative. Since then her lips have remained sensitive and she has had to use petrolatum periodically. About three years ago there began a series of flares, with failure of her lips ever to become normal. In addition, she has had numerous mild attacks of stomatitis and gingivitis.

Her mother, sister, and aunt suffer a similar condition but not quite as severe. Her maternal grandmother was also affected.

All types of diet and medication, including cortisone, have failed to produce material improvement. Vitamin B_{12} at times seemed to be beneficial. Flares have followed exposure to the sun, wind, and cold, to nylon, and turpentine, emotional upsets, and the ingestion of watermelon, coffee, beets, and roast beef. She also has periodic attacks of hives not related to any specific ingestant. She also has hay fever.

Patch tests were positive to pyrethrum and sodium arsenate. Roentgenograms of her sinuses and skull were normal except that the sella turcica appeared to be bridged by the clinoid processes. A blood cell count showed 11.5% eosinophiles, slight leucopenia (5,700), a low count of mature polymorphonuclear cells, 1,320 (normal, 3,600 to 3,900), and 2% myelocytes.

There is moderate edema of both lips, with slight scaling and telangiectasia.

Treatment with antihistaminic preparations, pilocarpine, riboflavin, cevitamic acid, para-aminobenzoic acid (PABA), quinacrine, gold compounds, and calcium gluconate have not been productive of any sustained or significant improvement.

DISCUSSION

DR. WILBERT SACHS: I believe it is a form of localized neurodermatitis with vesicles. I think there is a psychosomatic element but a psychiatrist would do more harm than good.

DR. PERRY SACHS: It might be atopic, but there is not enough evidence to establish this aspect of the diagnosis.

DR. JACK WOLF: I also believe the involvement of the lips is a manifestation of atopic dermatitis. The excellence of the response to cortisone is in line with this. While it is difficult to make this diagnosis on a single examination, the long course, the repeated recurrences, and the negative results following a most thorough search for possible contact causes, as well as the absence of a contact-type dermatitis, all favor the diagnosis of atopic cheilitis.

DR. SAMUEL M. PECK: I do not quite believe the cheilitis we see in this patient is a true part of the picture of atopic dermatitis. Let us say rather that children with atopic eczema have certain nervous habits, one of which is biting and pulling on their lips, which play a real role in its causation. Proof can be furnished by fitting a plastic appliance over the lips so that they are not able to traumatize them in any manner. Often it is the first step in healing such a condition.

DR. MAURICE J. COSTELLO: I agree with Dr. Sachs that it is a localized neurodermatitis. I think it is on a psychosomatic basis, and that she can be cured by prudent psychotherapy. I take it that all contactants have been ruled out. I have never seen lichen planus of the lips without lichen planus elsewhere in the mouth or on the body. Lichen planus doesn't look like this.

DR. FRANK C. COMBES: I still think this patient has atopic cheilitis or localized neurodermatitis, and the more I see of her the more I am impressed with the psychosomatic element. All contactants have been ruled out as well as they can be. There are lesions on the gums and oral mucosa, and several weeks ago there was a slight erosion on the border of the tongue. Not enough attention was given to the multifarious groups of ingestants to which she attributes the eruption. The flares are not consistent. Some have occurred during exces-

sive exposure to sun and wind. Periodically her eyelids will swell and she will itch all over for no apparent reason. Her sister is similarly affected to less degree and has been under the care of a psychiatrist, without benefit. I saw the sister once and the mother once. It is interesting also that the patient has a positive patch test to sodium arsenate, and she loves the color green. All her rooms are painted green. Scrapings have all been negative for pathogens. Trauma has been taken into consideration, and I wondered whether there was no rubbing. Except for one instance, she has not been able to leave aquaphor off her lips for the last two or three years, except last week when she used hydrocortisone ointment. There is a definite psychosomatic element that cannot be overlooked.

Tuberculosis Cutis Papulonecrotica (Papulonecrotic Tuberculids, Acnitis and Folliclis) Controlled by Isoniazid (Rimifon); Lichen Scrofulosorum; Tuberculous Adenitis, and Scrofuloderma. Presented by DR. MAURICE J. COSTELLO.

J. D., a Negro girl aged 9 years, was a patient at Seaview Hospital for one and one-half years in 1950 to 1951, and treated there for tuberculous adenitis and scrofuloderma. At that time it was found that she had fibrocalcific changes in the apices of the lungs. She had tuberculous phlyctenular keratoconjunctivitis, and residual scarring can be seen on the left cornea as a horizontal bar from 3 to 9 o'clock, which causes some visual impairment. The patient's mother died of tuberculosis when the patient was one year of age. Her grandaunt has sarcoid (Boeck) involving the face.

This patient was first observed at Bellevue Hospital a year ago. At that time, she showed numerous deep-seated nodules and necrotic papules on the lateral aspects of the forearms, elbows, and knees, which had been present for four years. She also showed on the left suboccipital region a group of closely aggregated yet discrete pinhead-sized, skin-colored papules. These were excised, and the histologic picture was that of lichen scrofulosorum. Discrete pinhead-sized, skin-colored papules were sparsely distributed on the face (acnitis).

Complete blood cell count showed hemoglobin 9.5 gm., red blood cells 4,500,000, white blood cells 8,600, with polymorphonuclear leucocytes 36, lymphocytes 54, and monocytes 4. Urinalysis was normal.

Treatment was begun in September, 1952, and consisted of isoniazid, 25 mg. twice daily, ferrous sulfate (Feosol), hexavitamins, and liver extract injections. Within a couple of months, all lesions on the arms and legs had undergone involution, and no new nodules appeared. Three months ago the patient stopped taking isoniazid while continuing to take ferrous sulfate and hexavitamins. Soon afterwards numerous deep-seated nodules and necrotic lesions again appeared on the arms and legs. Isoniazid was again instituted one month ago. As can be observed, the lesions have again undergone involution. Atrophic and pitted scars can be seen on the sites of previous lesions, and no nodules can be palpated.

DISCUSSION

DR. FRANK C. COMBES: It has been stated that the tuberculids do not customarily respond to isoniazid, whereas cutaneous tuberculosis does. That was a silly observation from my standpoint, as the tuberculids are dependent upon the presence of tuberculosis, either actually or previously active, so it is natural to expect improvement of the tuberculids with improvement of the tuberculosis. This case is an instance in which that has occurred. It is also probable that many lesions are referred to as tuberculids because of tuberculoid structures that are not tuberculids. These of course would not respond to isoniazid.

DR. JOHN W. DOUGHERTY: It may be that the focus of the tuberculid was in the scrofuloderma, and when the focus responded to isoniazid, the tuberculid cleared up. The patient may not have had any active pulmonary tuberculosis.

DR. WILBERT SACHS: The term "tuberculid" covers many different conditions, a small percentage of which are due to tuberculosis. The larger group has nothing to do with tuberculosis and will not respond to therapy.

DR. MAURICE J. COSTELLO: We presented this patient to show the several manifestations of tuberculosis in one person. She had tuberculous adenitis with scrofuloderma, and she had an active healed lesion in the lungs. When the isoniazid was discontinued, the disease recurred, and when it was reinstituted, the disease receded.

Pemphigus Erythematosus. Presented by DR. MAURICE J. COSTELLO.
Larva Migrans. Presented by DR. MAURICE J. COSTELLO.
Case for Diagnosis (Aphthous Stomatitis? Factitial Stomatitis?). Presented by DR. NATHAN SOBEL.

Thomas N. Graham, M.D., *President*
George M. Lewis, M.D., *Secretary*
Nov. 10, 1953

Argyria. Presented by DR. GEORGE M. LEWIS.

H. H., a boy aged 8 years, is presented from New York Hospital with a bluish discoloration of the face of four years' duration. There is no history of cardiac disease. Colloidal silver iodide (Neo-Silvol) nose drops were used over a four-year period in infancy, prior to the appearance of the pigmentation. The general health is good, but the child is subject to frequent upper respiratory infections.

There is a slate-blue discoloration about the mouth, nasolabial folds, and eyelids, with duskiness of the nail beds. The mucous membranes are normal.

The urine was normal except for a faint trace of albumin. The red blood cell count was 4,240,000, with hemoglobin 14.8 gm., and white blood cells 7,800. The hematocrit reading was 38%. X-rays of the chest were normal and studies for methemoglobinemia negative.

Biopsy showed the epidermis to be normal. Numerous rather immature hair follicles and only a few coil glands were visible. The collagen appeared normal. The blood vessels of the upper corium showed a few round cells and histiocytes in their adventitia. Scattered about the hair follicles and sebaceous glands and in the adventitia of the blood vessels were a moderate number of minute blackish granules. They did not appear to be present in the epidermis or the gland cells of the sweat and sebaceous glands but seemed rather to be in the endothelial and perithelial cells and in limiting membranes. Dark-field examination revealed the granules to be highly refractive. Diagnosis: Argyria.

DISCUSSION

DR. DAVID BLOOM: The most frequent cause of argyria is the use of mild silver protein (Argyrol). It is surprising to know that this drug is still being used by otolaryngologists and urologists.

DR. WALTER J. SCHMIDT (by invitation): Granules could be seen in some of the slides, but more by dark-field examination.

DR. GEORGE M. LEWIS: In order to develop argyria, a certain amount of silver must be absorbed. It is interesting that the pigmentation is always more noticeable on the exposed parts of the body, which again suggests photosensitization as one of the mechanisms by which the pigment is deposited, or at least made visually apparent. It is also of interest that, although the silver is deposited widely in the skin, it still is not visible except on skin exposed to ultraviolet rays. I do not believe that the mechanism has altogether been explained. One of our residents with argyria always looked better during the summer months when he was out in the sun. No therapy has any effect on the silver deposit in the skin. The best we can do is to give cosmetic aid.

Kaposi's Idiopathic Hemorrhagic Sarcoma. Presented by DR. GEORGE M. LEWIS.

B. C., a woman aged 52, of Jewish background, twisted her ankle three years ago, "breaking a blood vessel." Subsequently, swelling, dusky hue, and thrombophlebitis developed in the area. Since then the patient has noted increasing swelling, discoloration, and pain extending from the heel to the midcalf area. She has been treated with anticoagulants, paravertebral blocks, and other means, as if she had thrombophlebitis, on several occasions.

There is a sharply demarcated swelling extending from the carpophalangeal joints to the midcalf level, with a purplish-red to skin-colored mass of confluent tumefactions, blebs, or nodules evident. The eruption is most pronounced at ankle level. The plantar surface is uninvolved.

At Beth-El Hospital in 1952, a biopsy was said to show Kaposi's sarcoma, and roentgenograms were said to be normal.

Over a three-month period, the patient received 1,400 r of filtered x-rays (3 mm. Al) in weekly doses of 200 r at 30 cm. distance to two areas on the foot and ankle (lateral aspect), with slow but steady decrease in the size of the lesions. After seven months of relative comfort, the patient returned, again complaining of severe pain and recent increase in the size of the ankle, with many new lesions. Filtered x-ray therapy was again given, to a combined total of 2,500 r. Courses of penicillin of 1,200,000 units daily for 12 days resulted in decreased swelling and pain on three occasions temporarily. However, because of continued formation of blebs, pain, and edema of the ankle, unfiltered x-ray therapy was given, 150 r to three areas, with regression of some areas.

DISCUSSION

DR. ISADORE ROSEN: I should not be inclined to agree with the diagnosis on the clinical features presented tonight. There is a certain amount of lymphedema due to blocking of the lymph vessels. In my experience, it is unusual for this disease to be unilateral. As the patient was presented for therapeutic suggestions, I should not be inclined to administer any more x-rays. I have had satisfactory results in Kaposi's sarcoma with arsenic in the form of 2% sodium arsenate given subcutaneously. I suggest another biopsy.

DR. MAURICE J. COSTELLO: This must be some chronic lymph stasis with secondary infection. When Dr. Michelson was here last year, he explained that long courses of penicillin were of benefit. It is unusual to see Kaposi's sarcoma in a woman and also for it to be confined to a localized area.

DR. ORLANDO CANIZARES: Dr. Grispan in Argentina used penicillin therapy with good effect. At the Veterans Hospital we have tried it with indifferent results.

DR. JOHN W. DOUGHERTY: When this patient was first seen, the lesions and the histopathology were consistent with Kaposi's disease—more so than tonight. What you see now is the result of therapy.

DR. ANTHONY C. CIPOLLARO: I am not certain of the diagnosis. I should like to have another biopsy, because the predominating picture is that of lymph stasis and lymphatic vesicles. There are very few vascular elements in this type of tumor; so I should want to be convinced that we are dealing with Kaposi's sarcoma and not with chronic lymphedema with lymphangiomatous elements. Regarding the penicillin treatment, we used it in a small series at Polyclinic Hospital, and, although there was some temporary improvement, we got no results and stopped the treatment after carrying it out for almost six months. The only effectual treatment I know of is x-radiation, along with compression bandages to support the circulation. Of course amputation is effective, but it is too radical, even for a case like this. I have used nitrogen mustard without effect, and I have used arsenic without being impressed by the results; so I should be inclined to go along with the type of irradiation that Dr. Lewis has given, using various fields.

DR. GEORGE C. ANDREWS: I also have some doubt about the diagnosis. It may be that the patient has Kaposi's disease but it is unusual to see it in a woman and also to have it unilateral. Sometimes there are vesicular or bullous lesions in Kaposi's disease. Clinically, the condition is more like lymphangioma circumscriptum. I think there should be more study and conservative treatment, as she has had pretty large doses of irradiation already. I believe elastic bandages should be used, as Dr. Cipollaro suggested.

DR. JACK WOLF: My thoughts regarding the diagnosis are very much like those of Dr. Cipollaro. I did not see any lesions characteristic of sarcoma. Some are hemorrhagic and superficial and resemble somewhat a purpuric type of eruption occasionally encountered on the feet and legs. Before one proceeds with more therapy, another biopsy is indicated, so that more irradiation will not be given where it will do no good.

DR. WILBERT SACHS: I cannot see how you can get lymphedema around the ankle without involvement of the toes.

DR. ANTHONY C. CIPOLLARO: I accept the correction; I should say lymphectasia.

DR. ADRIAN BRODEY: I believe there are sufficient clinical findings to substantiate the diagnosis of Kaposi's sarcoma and that the treatment of choice would be further x-ray irradiation.

DR. GEORGE M. LEWIS: The clinical improvement has changed the appearance so that it is understandable that some doubt should exist as to the diagnosis. I am a little prejudiced because the earlier signs were more definite. Still, it is unusual to see the disease in a woman and unilaterally. The predominant symptom was pain, which is now much relieved. X-rays gave symptomatic relief. Also, three courses of penicillin that were administered produced slight betterment in her condition. The suggestion of another biopsy will be followed.

NOTE: The pathologic findings in the second biopsy were similar to those in the first, substantiating the diagnosis of Kaposi's sarcoma and revealing no evidence of lymphosarcoma.

Sturge-Weber Syndrome Associated with Unilateral Cutaneous and Osseous Sarcoidosis. Presented by DR. DAVID BLOOM.

G. M., a Negro girl aged 12, was seen for the first time at the Sydenham Skin Clinic in October, 1953.

The patient presents a nevus flammeus involving the right side of the face, which is larger than the left, with an irregularly shaped plaque on the right cheek suggesting a nevus anemicus. The right eye protrudes, and there is an operative coloboma of the iris. The patient shows a left hand-drop and is unable to extend the left elbow. There is some paralysis of the left lower extremity, as she drags the left leg when walking. On the left side of the face there are depigmented spots with a dark red dot in the center, which on palpation reveal a pea-sized subcutaneous nodule attached to the skin. Another such lesion is present on the left arm and still another on the left thigh.

The patient was born at full term in 1941. At birth it was noticed that she had a nevus flammeus on the right side of the face and a protruding eyeball, which was diagnosed as buphthalmos and for which she was operated on soon after birth. At the age of 6 months, she developed convulsions involving the left side of the body which left her with a drop-hand, inability to extend the left elbow, and paralysis of the left lower extremity. Since then the child has had daily convulsions, lasting from two to five minutes.

The white spots on the left side of the face, arm, and thigh appeared in February of this year. In the course of our observation during the past few weeks, the nodules have diminished in size.

The child is mentally retarded but attends school.

At the age of 6 months, a lumbar puncture revealed a 3+ Pandy reaction and 173 mg. of total protein. A roentgenogram of the skull did not show any definite abnormality, but one taken recently showed wavy calcifications conforming to the cerebral convulsions over the right side of the brain, extending from the occiput to the posterior frontal region. The pattern of calcifications was considered by the roentgenologist as characteristic for Sturge-Weber syndrome with extensive cerebral hemangioma. There was no evidence of increased intracranial tension. The calvarium was thickened on the side of the lesion. There was some plagiocephaly, the head being larger on the left side than on the right.

DISCUSSION

DR. ORLANDO CANIZARES: The depigmentation on the face is hard to explain. I first thought it a nevus anemicus, but it would seem the lesion is peeling off and leaving normal skin.

DR. JACK WOLF: Some manifestations of the disease are well understood and need no discussion. However, the new lesions which have developed on the left cheek and on the arm are unusual. No clinical diagnosis is possible at this time, but histologic examination will probably provide the answer. I am not impressed with the diagnosis of multiple hemangiomas.

DR. GEORGE C. ANDREWS: We are indebted to Dr. Bloom. The hypertrophy of the right cheek may fit in with the hypertrophic hemangiectasis, which is usually found on the limbs but may affect the face. I agree with Dr. Canizares about the patch spoken of as nevus anemicus. As for the white patches on the left cheek and thigh, I did not palpate much thickening and they suggest the white spots found in Negroes, achromia streptogenes. The borders are not sharp but merge off into normal skin. This is an excellent example of Sturge-Weber syndrome. I have had two cases lately, one at Vanderbilt Clinic and another at the office, a child about 4 years old.

DR. DAVID BLOOM: The depigmented lesions appear as Sutton's leucoderma centrifugum. However, on palpation there is a pea-sized induration in each lesion. Because of the vascular nevus on the face, this induration was thought possibly to be an angioma. The hemihypertrophy of the face and skull has been reported in other cases of Sturge-Weber syndrome.

NOTE (Jan. 12, 1954): Biopsy of a lesion on the left thigh showed the structure of sarcoid. In view of this finding, tuberculin tests were performed and roentgenograms of the chest, hands, and feet made. The intradermal tuberculin test on the right and left arms gave no reaction. The roentgenogram of the chest showed enlargement of the superior mediastinum to the right, with right paratracheal adenopathy. There was no pulmonary infiltration. Roentgenograms of the hands revealed pathologic changes only in the left hand, where there were several small cystic lesions in the proximal and middle phalanges, the largest being at the distal end of the proximal phalanx of the second finger. In several phalanges, there was also disorganization of the trabecular pattern, most pronounced in the middle phalanx of the fourth finger. Although some soft tissue swelling was noted about the proximal phalanx of the second and about the middle phalanx of the fourth finger, no periosteal reaction was seen along the phalanges. The bones of the feet showed no abnormality. In view of the cutaneous and bony changes and the tuberculin anergy, the roentgenologist interpreted the chest findings as those of sarcoidosis, although the unilateral mediastinal adenopathy is considered unusual in sarcoidosis.

Case for Diagnosis (Bullous Leukemid? Dermatitis Herpetiformis?). Presented by DR. ORLANDO CANIZARES.

S. G., a man aged 63, is presented from the Bronx Veterans Administration Hospital with an eruption on the legs of 10 weeks' duration.

About 10 weeks ago, the patient suddenly developed edematous, purplish-red plaques on the trunk, scalp, and extremities, on which bullae developed. The entire plaque would fade in several days, leaving the bulla. In addition, bullae appeared on the scalp and legs out of clear skin. These have slowly subsided with no specific therapy. At present he has only an occasional bulla arising out of clear skin on the legs.

In October, 1950, the patient developed a generalized eruption diagnosed as dermatitis medicamentosa. At the time a diagnosis of chronic lymphatic leukemia was made on the basis of peripheral blood and bone marrow studies. The eruption subsided in two weeks, but he was left with a residual dermatitis of the legs for seven months. He states that since then he has also had an occasional blister on his legs.

The patient developed ophthalmic herpes zoster in 1952, at which time he showed no evidence of a bullous eruption. Bone marrow and peripheral blood studies were compatible with a diagnosis of chronic lymphatic leukemia. He received no specific therapy, but there has been a gradual lowering of the peripheral white blood cell count, although he still has adenopathy of the axillae and groins.

Laboratory data: Jan. 1, 1952—RBC 3,640,000; WBC 63,200, with 17% polymorphonuclear leucocytes, 78% lymphocytes, 2% monocytes, and 3% juvenile cells. March 26, 1952—RBC 2,730,000 (intestinal bleeding due to duodenal ulcer at this time); WBC 24,400, with 17% polymorphonuclear leucocytes, 78% lymphocytes, 4% monocytes, and 1% eosinophiles; platelets, 84,000. Oct. 6, 1953—RBC 4,500,000; WBC 10,950, with 45% polymorphonuclear leucocytes, 30% lymphocytes, 5% monocytes, 18% eosinophiles, and 2% basophiles.

Biopsy of the skin was compatible with dermatitis herpetiformis, with eosinophilic infiltrate in the cutis and extending into the subcutis.

DISCUSSION

DR. DAVID BLOOM: As the biopsy does not reveal lymphatic leukemia in the bullous lesions, they must be considered a leukemid, a toxic reaction seen in lymphatic leukemia. I do not believe this patient has dermatitis herpetiformis.

DR. WILBERT SACHS: To me, the picture of this slide is that of dermatitis herpetiformis, regardless of what else the patient has. I do not doubt the diagnosis of lymphatic leukemia, but he also has dermatitis herpetiformis.

DR. ANTHONY C. CIPOLLARO: Has this patient had lesions elsewhere on the body than the lower extremities?

DR. ORLANDO CANIZARES: Yes, on the scalp and trunk. Because of the histologic picture we began the administration of sulfapyridine. There has been no benefit for two weeks, but we are going to continue its use. We believe that the condition is a toxic eruption due to leukemia.

Vasculitis Consistent with Erythema Induratum. Presented by DR. JOHN W. DOUGHERTY.

V. P., an Italian man aged 60, in the United States for 44 years, had a tuberculous cervical node removed at Post-Graduate Hospital 37 years ago. Fifteen years ago he first noted an eruption on the legs which was diagnosed as tuberculosis of the skin at the New York Skin and Cancer Hospital. The leg lesions have recurred repeatedly, appearing first as a swelling, then becoming red, and finally draining for several weeks. At one time he had phlebectomy for these lesions. For two years he was treated with corticotropin (ACTH), cortisone, typhoid vaccine, and penicillin for optic neuritis, and during this time the leg lesions were in remission. In 1949, a ganglion was removed from the right wrist, with the diagnosis of tenosynovitis. This recurred six months ago. For six months, there has been swelling of the left knee and left ulnar styloid. On Oct. 21, 1953, the left ulnar styloid and adjacent soft tissue were removed and 100 cc. of yellow fluid aspirated from the left knee. A red nodule was removed from the right leg for biopsy.

Both legs show extensive, deep scarring, anteriorly and posteriorly. There is a healing, ulcerated area covered by a thick crust on the left calf. On the right calf there is a biopsy scar at the site of an indurated, inflammatory nodular area which had seemed to show early fluctuation prior to biopsy.

Roentgenograms of the chest were normal. Roentgenograms of the lumbosacral spine showed old tuberculosis involving the body of L3 with partial collapse and evidence of repair, with bridging between L2 and L3. The erythrocyte sedimentation rate was 24, and the Mazzini reaction negative. Culture of the fluid aspirated from the right knee shows no growth as yet.

Biopsy from the right calf showed the epidermis to have slightly patchy hyperkeratosis and follicular plugging. The basal layer was intact. A large area in the deeper corium and subcutaneous fat showed necrosis and was surrounded by a granulomatous and tuberculoid reaction consisting of fibroblastic proliferation and epithelioid hyperplasia showing numerous giant cells, many of the Langhan's type. Foci tended to be about the sebaceous glands and blood vessels and extended deep into the fat trabeculae. The upper corium was less involved but did show a few foci close to the epidermis. Numerous lymphocytes and occasional plasma cells, eosinophiles and polymorphonuclear cells were scattered throughout. Most of the smaller and larger arterioles showed extreme thickening of their walls with marked subendothelial proliferation and obliterating endarteritis. Acid-fast stain revealed no organisms. Diagnosis: Vasculitis consistent with erythema induratum.

DISCUSSION

DR. WILBERT SACHS: The microscopic picture is that of Bazin's disease.

DR. ISADORE ROSEN: It is unusual to see Bazin's disease in men, especially at 63. The diagnosis was made histologically, but clinically it suggests an ulcerative form of tuberculosis. Bazin's disease occurs mostly in young girls on the posterior surface of the legs.

DR. PAUL GROSS: He has tuberculosis of the skin and apparently has a tuberculous focus in the knee. With this type of lesion it is not unusual to find tuberculosis of the hypoderm,

and this would be proved if the tubercle bacillus could be demonstrated. I don't want to object to the diagnosis of Bazin's disease because the patient is male, but, as Dr. Rosen says, the whole clinical picture is more suggestive of another type of tuberculosis.

DR. DAVID BLOOM: Has anyone here seen typical Bazin's disease in a man this age?

DR. GEORGE C. ANDREWS: I think Dr. Gross's and Dr. Rosen's remarks have been very much to the point.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Fred F. Feldman, M.D., *President*

Irving A. Lewe, M.D., *Vice-President*

Harold Price, M.D., *Secretary*

Dec. 29, 1953

Acrosclerosis. Presented by DR. CHARLES SHERTER.

M. G., a 39-year-old white woman, states that for the past six years her fingers would become "tender, swollen, and purplish" if she handled cold wave solutions in her work as a beauty parlor operator but would clear in a few days if these items were avoided. However, in January, 1953, she noticed definite stiffness of the fingers, associated with tingling and numbness of the fingertips. This continued until July, 1953, when brown discolorations appeared about the elbows, knees, arms, thighs, buttocks, and ankle areas with definite stiffness in the above-mentioned joints and also in the skin. She also complained of some difficulty in swallowing and shortness of breath. When she was first seen in November, 1953, physical examination revealed a well-developed, well-nourished woman with a suggestion of "ironed-out" facies. General medical examination revealed no significant abnormalities. The skin of the fingers is smooth, shiny, tense, and mottled in color. The terminal phalanges are tapered, and the skin is relatively hard and bound fast to underlying structures. The skin in these areas is somewhat moist and cool. Proximally, there is less induration. Mottled areas of brownish hyperpigmentation with varying degrees of induration are also present about the elbows, arms, axillae, neck, chest, buttocks, thighs, legs, ankles, and feet.

A hemogram, urinalysis, N.P.N., uric acid, creatine and creatinine, x-ray of esophagus and chest, and an electrocardiogram were within normal limits. The sedimentation rate was slightly elevated. Biopsy of skin taken from the thigh showed changes compatible with the clinical diagnosis of scleroderma. The muscle tissue from the thigh was normal.

Treatment was started with cortisone orally—100 mg. a day in divided doses for two weeks, then 150 mg. a day for another two weeks. During this time there has been a definite reduction in induration, especially of the fingers, and the symptoms such as tenderness, tingling, numbness, etc., have abated considerably. In the past two weeks pentaerythritol tetranitrate (Peritrate)—10 mg., q.i.d. was added orally to the cortisone regimen for its possible vasodilating effect, and cortisone was reduced to 37.5 mg., q.i.d.

DISCUSSION

DR. MEYER BERKE: This is classical acrosclerosis with typical sclerodactylia and history of preceding Raynaud's phenomena.

DR. ANITA GELBER: I would like to ask Dr. Rattner if he and the group in Chicago are using diuretics along with cortisone.

DR. HERBERT RATTNER, Chicago (by invitation): I myself employ diuretics when patients require steroid therapy for more than just a few days time.

DR. HAROLD C. FISHMAN: I would like to ask Dr. Rattner his opinion of the value of cortisone therapy for scleroderma. The Mayo Group indicate that they have given it up. Some of us have seen good results.

DR. HERBERT RATTNER, Chicago (by invitation): Our results at the Cook County Hospital have been disappointing. In some cases it seemed to aggravate the condition. I cannot speak

from experience. The recent report from the Lahey Clinic in the *Journal of the American Medical Association*, in which they recommend operations more extensive than have hitherto been practiced, was the most favorable report I've read. Previous reports have not been encouraging.

Granuloma Annulare? Presented by DR. FRED F. FELDMAN.

Mrs. P. C., a 35-year-old white housewife, first noticed the onset of papules on the anterior surface of her right leg three years ago. There has been a gradual increase in the number of lesions. There is no pruritus associated with the eruption. Physical examination, a complete blood count, and two recent urinalyses have been essentially normal.

The patient's dermatosis is confined to the pretibial area of the right leg. The lesions are discrete, firm, reddish-brown papules, varying from 1 to 5 mm. in diameter.

Histologic examination reveals a thin epidermis without significant change. There are marked degenerative changes in the corium. The collagen is lumpy and takes a basophilic stain. There is degeneration of the elastica. Focal round cell infiltration is seen around hair follicles. An elastic fiber stain shows degeneration of elastic tissue.

DISCUSSION

DR. HAROLD C. FISHMAN (Comments on Slide): This is one of the most interesting cases that I have seen in a long time. I believe it is a collagenous nevus of Lewandowsky, a very rare naevus tardus.

DR. FRED F. FELDMAN: The classic histologic picture of granuloma annulare is not always seen—even in some cases that are typical clinically. In view of the findings we have to date, I feel the diagnosis as presented is the most likely one. The pathologist described collagenous degeneration and she felt that the histologic changes were compatible with the diagnosis of granuloma annulare. I plan to repeat the biopsy and also get additional stains.

Epidermolysis Bullosa—Acquired (?) Presented by DR. HAROLD PRICE.
Case for Diagnosis. Presented by DR. DAVID N. ALCON.
Case for Diagnosis: Erythema Multiforme-Chronic Type? Presented by DR. CHARLES SHERTER.
Case for Diagnosis: Gumma? Presented by DR. STANTON B. MAY.

NEW YORK DERMATOLOGICAL SOCIETY

George C. Andrews, M.D., *President*

Gerald F. Machacek, M.D., *Secretary*

Nov. 24, 1953

Case for Diagnosis (Nevoxanthoendothelioma? Urticaria Pigmentosa?). Presented by DR. GEORGE M. LEWIS.

J. T., a girl aged 5 months, was born at term and has been healthy. At 6 weeks of age, a flat, brown lesion was noted on the left side of the forehead. This became elevated and firm and has been asymptomatic.

There is an elevated, circinate and ovoid, freely movable lesion on the left side of the forehead, 8 mm. in diameter. It is yellowish-brown in color. The surface is rough and resembles orange peel. Nothing was seen on transillumination. The lesion has been observed for two months and has not increased in size.

DISCUSSION

DR. JOHN C. GRAHAM: I agree that it is nevoxanthoendothelioma rather than urticaria pigmentosa.

DR. WILBERT SACHS: I agree with the diagnosis. The clinical picture fits in so well that there is no indication for a biopsy. That can always be done later if necessary.

DR. MAURICE J. COSTELLO: I would be inclined to the diagnosis of nevoxanthoendothelioma. There is no urtication on rubbing, which is quite commonly seen, even in a single lesion of urticaria pigmentosa. I don't think anything would be lost by taking a small biopsy. The patient may have other lesions, in the bones, for instance.

DR. EUGENE F. TRAUB: Biopsy can be performed by a simple excision. A hairline excision would give a good cosmetic result. If the diagnosis is wrong, it would be known at this point.

DR. GERALD F. MACHACEK: Every indication here is that it is nevoxanthoendothelioma. I would be inclined to wait, but that is a question of judgment. If the lesion does not seem to be regressing or the mother is particularly upset, it could be excised later.

Nodular Vasculitis (Majocchi's Disease). Presented by DR. FRANK C. COMBES.

H. H., a woman aged 29, has had a painful eruption on the ankles and feet for two and one-half years. There are occasional "swellings" over the areas of involement, accompanied by shooting pains running down the lateral and medial aspects of both legs. The past history is essentially negative except for a mild hypochromic anemia and pallor with numbness of the hands in cold weather and on immersion in cold water.

Examination shows hyperpigmented, gyrate, ringed, nonelevated areas with hypoesthetic centers over the external and internal malleoli. Some punctate purpuric areas were noted on the first visit. Since the patient was first observed several small spontaneous ulcerations have been noted, and new purpuric lesions have appeared about the malleoli. The pains along the outside of the leg have diminished and are more common on the medial aspect. The patient states that occasionally the pain starts in the hip and travels peripherally. On examination there is no tenderness along the sciatic nerve.

Histologic examination showed chronic dermatitis with vasculitis. Neither melanin nor hemosiderin were present, and there was no hyalinization of the small vessels. Histamine flare tests were normal, as were also the moccasin venom and Rumpel-Leede tests. The blood cell count on June 1, 1953, showed 4,000,000 red blood cells, with 94% hemoglobin. There were 4,700 white blood cells, with 50% polymorphonuclear leucocytes, 41% lymphocytes, 2.5% monocytes, 5% eosinophiles, and 0.5% basophiles.

DISCUSSION

DR. GEORGE M. LEWIS: I don't know much to discuss in a case of this type. The histology is often very confusing and I don't know any definitive treatment.

DR. WILBERT SACHS: There is little doubt that this is vasculitis, but I would not call it a nodular vasculitis. It is not deep enough and is not nodular.

DR. J. LOWRY MILLER: She has changes around the foot, possibly explainable by the fact that she lived in Norway and was exposed to the cold for a long period. I have shown a different type of case, with purpuric lesions which appear first on the lower extremities around the ankles and spread upwards. I don't believe anyone has described or given a name to this disease. The lesions come and go. Fever apparently clears them up temporarily, but they reappear. Histologically, vasculitis is present. The case under discussion is clinically different, and I thought I could see a little atrophy. I agree with Dr. Combes that this shows more than a vasculitis. It may be a beginning Majocchi's disease, perhaps precipitated by exposure to cold.

DR. MAURICE J. COSTELLO: As Dr. Miller brought out, the patient had cutis marmorata of the feet and legs, and certainly impairment of circulation is connected with the disease. I think isoniazid (Rimifon) is a simple and safe type of treatment that would be worth while, with supportive dressings and elastic stockings.

Tick Granulomas. Presented by DR. EUGENE F. TRAUB.

DISCUSSION

DR. GERALD F. MACHACEK: Many of these cases we think are so obvious clinically are diagnosed as lymphoblastoma. It is remarkable how closely they simulate that picture; one would even think of carcinoma.

DR. J. LOWRY MILLER: I recall one case treated successfully by sticking into the lesions a sharp stick dipped in phenol. This actually produced a little draining sinus through which the head of the tick worked its way out with resultant cure.

DR. JOHN C. GRAHAM: It is a beautiful demonstration of what shouldn't be done. Pulling the tick off produced the lesions. They are not the result of the bite, but the head remains under the skin. One should never pull off a tick. A cigarette, alcohol, or cleaning fluid will usually loosen it.

DR. FRANK E. CORMIA: If it is true that the cause is just the head of the tick, biopsy punch would remove the lesion.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Bertram Shaffer, M.D., *Chairman*

Lewis M. Johnson, M.D., *Secretary*

Feb. 19, 1954

Late Secondary Syphilis; Early Manifestations Probably Submerged by a Single Small Dose Injection of Penicillin. Presented by DR. THOMAS BUTTERWORTH and DR. JOHN E. GERMAN, Reading, Pa.

K. N., a white youth, aged 20, presented comparatively few copper-colored, brownish, or violaceous papules on the forehead, nose, trunk, penis, scrotum, palms, and soles. The skin about the anus and in the third interspace of the right foot was white and sodden. There was diffuse scaling of the scalp with no loss of hair.

On Oct. 26, 1953, the patient developed bilateral inguinal adenopathy. The nodes are said to have been discrete, firm, and slightly tender. He was given 400,000 units of S. R. penicillin (each cubic centimeter with aqueous diluent contains 300,000 units crystalline procaine penicillin G). On Oct. 27, 1953, he had headache, chills, and fever (Herxheimer reaction?). On Jan. 29, 1954, the cutaneous manifestations appeared.

The patient's preemployment physical examination and serologic tests for syphilis were negative; urinalysis and complete blood cell count were within normal limits. Physical examination by the presenters disclosed generalized adenopathy, sparing the epitrochlears. There was noteworthy enlargement of the occipital glands.

The Kolmer Wassermann reaction was 4+; the VDRL, reactive.

DISCUSSION

DR. REUBEN FRIEDMAN: I would say that the multiple interdigital lesions on the feet strongly suggest tinea pedis. However, I do want to call attention to the possibility that patients may appear with what seems to be "athlete's foot" but which turns out to be ulcerative or condylomatous lesions involving the interdigital webs. I had a patient recently (reported in the *Delaware M. J.* **25**:127-132 [June] 1953, and in the *J. Nat. A. Chiropodists* **44**:15-35 [Jan.] 1954), referred by a chiropodist, who presented a deep ulcer in the fourth web of the right foot. Were it not that there was a papulosquamous eruption on the plantar aspect, a papular eruption on the palms, and circinate lesion at the right nasolabial junction, the possibility of syphilis might have been overlooked. I did a dark-field examination of the exudate and found it loaded with Treponema pallidum. Not long ago Dr. H. T. Dexter (A. M. A. ARCH. DERMAT. & SYPH. **63**:581-585 [May] 1951) reported two cases in which the systemic diagnosis of syphilis was made on the basis of interdigital lesions of the feet which on examination proved to be dark-field-positive. She also reported eight other cases of syphilis which had dark-field-positive foot lesions. This presents the possibility of even a patient's feet being the source of innocently acquired syphilis by physicians and chiropodists. I should like, therefore, at the moment to recall the well-known fact that early and late plantar syphilids may be mistaken for "athlete's foot."

DR. HERMAN BEERMAN: In "Modern Clinical Syphilology" there is a picture of such a case, which I reported. Dr. Samuel Bluefarb, of Chicago, was one of the first to describe this lesion.

DR. IRA L. SCHAMBERG: In 1947, more than 2,000 patients with primary and secondary syphilis were reported to the Health Department in Philadelphia. In 1953, there was a total of 88 cases, a decline of 95%, which is a little better than the 90% decline in the country at large.

When I hear of cases of early syphilis appearing in dermatology clinics, I sometimes wonder whether they are reported promptly to the Health Department so that epidemiologic investigations may be carried out. They should be reported by telephone, in order that a member of our epidemiological staff can go to the clinic and interview the patient immediately.

DR. THOMAS BUTTERWORTH, Reading, Pa.: When we saw this patient a week ago, there were half a dozen lesions on his forehead, nose and cheeks; three classic copper-colored papules on the left side of his trunk, about half a dozen papules on the penis and scrotum, three on the palms, and two on the soles. This is the cutaneous relapse picture, but if I were to label this "cutaneous relapse," it would imply that the patient had had a previous eruption. When we examined him this afternoon by daylight, he had a roseola; so we are undecided as to just how we should classify the case. Last week we thought it was in the late stage, wherein a comparatively few lesions are limited to small portions of the body; now he has this roseola which shows up in daylight.

DR. JOHN L. MULHERIN: We must consider the interdigital erosion as a primary lesion in this type of case. I collaborated in the report of a series of 20 cases of extragenital chancres several years ago and we reported a primary lesion appearing between the first and second toes which was not unlike that of tinea pedis.

Lichen Planus with Widespread Subungual, Palmar, and Plantar Lesions. Presented by DR. JOHN E. GERMAN, Reading, Pa.

A. H., a white man, aged 45, stocky, well nourished, presented a tender, confluent, papular eruption on the thenar and hypothenar areas of both palms and over the palmar surface of the distal phalanges, with a milky appearance of the fingernails. On the longitudinal arch of each foot was a similar papular confluent eruption, which caused the patient discomfort. There were numerous scattered violaceous plaques on the ankles, wrists, and arms, and the upper part of the back, many in lines of excoriations. On the penis there were violaceous erythematous papules on the glans and prepuce, together with many bullae and vesicles. These latter may have been due to a previous ointment.

In November, the patient saw his chiropodist, who had been treating him for plantar hyperkeratosis and noted no other symptoms or any other condition. Thereafter, the patient developed tender and painful lesions on the insteps of both feet and on the palms. These spread to the ankles and wrists and then to the penis and back.

Culture of scrapings of the hyperkeratoses on the feet and portions of nails failed to reveal any fungus growth after six weeks. Potassium hydroxide and lactophenol examinations of scrapings revealed no mycelia or spores.

The patient has been treated by: (1) rest, (2) a shake lotion for the pruritis of the body, (3) phenobarbital, ¼ grain (15 mg.) four times daily and acetylsalicylic acid, 5 grains (0.3 gm.) four times a day, (4) alternating injections of bismuth and vitamin B_{12} weekly, (5) 3% salicylic acid and ammoniated mercury ointment to the hyperkeratotic papules of the palms and soles, and (6) zinc oxide paste (Lassar's paste) applied locally to the glans and prepuce.

DISCUSSION

DR. JOHN E. GERMAN, Reading, Pa.: About the end of December, this patient was still complaining of pain in his hands; the lesions were tender, and I thought I should like to see the results of quinacrine (Atabrine) in a case of lichen planus. Within three days, while he was taking 3 tablets a day, he developed new lesions on his buttocks and thighs. I immediately stopped the quinacrine, resumed the bismuth therapy, and kept him on sedation therapy. He is improving at present.

DR. BERTRAM SHAFFER: Had he ever received quinacrine before?

DR. JOHN E. GERMAN, Reading, Pa.: No. He also denied taking acetylsalicylic acid, acetophenetidin, phenolphthalein, or any of the common medications.

DR. REUBEN FRIEDMAN: I am skeptical of the diagnosis of lichen planus of the patient's nails. Were he to have walked today into a dermatological clinic or office presenting only the picture he does on the fingernails and toenails, I do not think anyone would even dream of a

diagnosis of ungual lichen planus. We see lichen planus often and involvement of the nails very infrequently, and when we do it does not at all resemble what we see here tonight. I think that, even though the scrapings and cultures have been negative for fungi on several occasions, I should not care to accept the reports as conclusive.

DR. ALBERT M. KLIGMAN: I would be one of those who, by simple observation, would not think this was ringworm of the nails. I think that if one looks for involvement of the nails in persons who have known lichen planus, one certainly would not see the condition that is seen here tonight, but one does see lesions that indicate lichen planus. The fact is that the pathogenesis of ringworm of the nails is such that the fungus begins by invading the nail bed and secondarily throws up the nail, causes overriding of the secondary nail bed on the plate, so that the proximal portion of the nail is rather free. Under the posterior nail fold, even in long-standing ringworm, the fold is seen to be relatively intact. In fungus infections we are dealing with a disease primarily of the nail bed which secondarily mutilates the nail plate; in lichen planus we are dealing with a disease of the nail plate which secondarily damages the nail bed.

DR. CARROLL F. BURGOON: I showed Dr. German pictures of a girl whose fingers we could have superimposed on this man's, and the nail changes were exactly the same. When we saw her nails we wondered whether they were dystrophic or related to her lichen planus, and after seeing this patient tonight, I am inclined to believe that these changes are related to the lichen planus.

DR. JOHN E. GERMAN, Reading, Pa.: When I first saw this man he had all the evidences of lichen planus, and I was particularly interested in the nail changes. I performed three cultures which were negative over six weeks for fungus infection; I scraped the nail beds and used KOH preparations three or four times; each was negative for any form of growth. It is unusual in a mycotic infection to have all 20 nails involved at the same time.

DR. ALBERT M. KLIGMAN: There is one clinical concept here which is worth noting: These atrophic changes are a Köbner phenomenon in a patient with lichen planus. After all, the nails suffer much trauma in the ordinary course of life.

Basal Cell Cancer, Cicatricial, Resulting from Branchial Cyst? Presented by DR. H. E. TWINING.

M. K., a white woman, aged 21, about three years ago developed a small lesion on the right side of her neck. This gradually increased in size to 5 by 4 cm. before operation. She complained of occasional bleeding and a sensation of itching and tingling. At the first examination by the presenter, on Nov. 23, 1953, the lesion gave the impression of a localized scleroderma. The border was sharply demarcated, slightly elevated, and erythematous. The central area was definitely hard on palpation and contained a small encrusted ulceration measuring 0.75 cm. in diameter. Just beneath the ulcer was a hard, palpable subcutaneous nodule 0.5 cm. in diameter. On Feb. 8, 1954, the lesion was excised, and a fibrous band extended upwards about 2½ in. (6.2 cm.) was dissected.

The complete and differential blood cell counts were within normal limits. The serologic tests for syphilis were negative.

The report on the biopsy specimen, taken partially from the ulcer, was basal cell cancer, cicatricial.

DISCUSSION

DR. H. E. TWINING: When I first saw this woman, she had had the lesion for about five years and nothing had been done. It was very suggestive in the beginning, except for the erythematous, slightly raised border, of a localized scleroderma, except that it had a small ulceration in the center of this lesion and that just beneath it, about a centimeter or two, there was a small nodule. After learning that histologically it was a basal cell cancer (of the cicatricial type), I sent her to a plastic surgeon. He thought that there might be a possibility that something caused the ulceration and started the dissection from the bottom, and when he got in near the growth he found a fibrous band which he feels is definitely the result of a branchial cyst. The biopsy reports we have verify Dr. Weidman's diagnosis of basal cell cancer. If this is a basal cell cancer and is caused by a branchial cyst, it is the first I have ever heard of.

DR. IRA L. SCHAMBERG: This patient reminds me of a 32-year-old man whom I saw with a lesion in the identical area. Histologically, that too was a basal cell cancer. I excised that one myself. It seems rather an unusual location for basal cell cancer, and also both of these patients are relatively young. I should be interested in the pathologist's opinion as to what the relation might be to a branchial cyst.

Epidermolysis Bullosa, Congenital Dystrophic Type. Presented by DR. HERBERT M. LEAVITT, Easton, Pa.

N. M., a white youth, aged 20, with no family history of cutaneous disease, presented scattered small, superficial, bullous lesions on the hands and feet, especially over bony prominences, such as the malleoli. There were deformities, scaling, and contracture of the fingers and toes, with loss of the nail plates. The healed areas were covered by thin, atrophic skin.

From early childhood the patient had had a continual series of vesicular and bullous lesions on the upper and lower extremities. Many of these lesions had been infected, failing to heal promptly, and leaving scars and atrophy. The disease has not responded to various forms of therapy given by dermatologists in Cincinnati, Baltimore, and New York City. Deformities of the fingers and toes gradually developed over a period of many years.

The patient was treated by the presenter with hydrocortisone ointment for about a week, on the hands. The result was inconclusive.

DISCUSSION

DR. HERBERT M. LEAVITT, Easton, Pa.: There is a special reason for presenting this young man. He is a college student, eager to get married in the near future, and he has consulted dermatologists in different cities. All have advised him against getting married, but he is still looking for one who will tell him that it is proper. I present him tonight to learn whether anyone can tell him that he can get married and his children will not have this disease. As far as he knows, no one else in his family has this disease.

DR. ALBERT M. KLIGMAN: This type of disease is the recessive type, in which there is no history of the disease in the immediate background of the patient, nor it is very likely, in fact it is very unlikely, that this man's children will have the disease unless he marries a woman with the recessive type in her background. The situation is quite different with the dominant type, in which one of the parents always has the disease and in which 50% of the children also acquire the disease. The pattern is so clear-cut here that we ought to think in terms of structure rather than terms of disease. This is the recessive type of the disease, which means that there is no immediate antecedent in the family with the disease and also that the patient can get married with the likelihood that his children will be normal.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I agree with Dr. Kligman. Fortunately, most people with hideous diseases such as this cannot find a mate; so they tend to breed out. We must remember that there is a dominant as well as a recessive type of dystrophic epidermolysis bullosa.

Exfoliative Dermatitis; Chronic Lymphatic Leukemia. Presented by DR. CARROLL F. BURGOON and (by invitation) DR. QUENTIN R. CONWELL.

Acute Disseminated Lupus Erythematosus (Cutaneous and Systemic). Presented by DR. H. E. TWINING, DR. CARROLL F. BURGOON and DR. LOUIS JAFFE.

Lupus Erythematosus? Lichen Planus? Presented by DR. H. E. TWINING.

Lichen Planus. Presented by DR. CARROLL F. BURGOON and (by invitation) DR. QUENTIN R. CONWELL.

Sarcoidosis. Presented by DR. DOROTHY R. LYNN.

Scleroderma. Presented by DR. CARROLL F. BURGOON.

Linear Scleroderma. Presented by DR. HERBERT M. LEAVITT (Easton, Pa.).

Lichen Sclerosus et Atrophicus. Presented by DR. HERMAN KLINE (Atlantic City, N. J.).

Necrobiosis Lipoidica Diabeticorum with Ulceration. Presented by DR. LESLIE NICHOLAS.

Drug Eruption of Both Fixed Type and Erythema Multiforme Type. Presented by DR. LESLIE NICHOLAS and and DR. CARROLL F. BURGOON.

A Case for Diagnosis. Presented by DR. CARROLL F. BURGOON.

Sarcoid. Presented by DR. DOROTHY R. LYNN.

Urticaria Pigmentosa. Presented by DR. LOUIS JAFFE and (by invitation) DR. JOHN MARON and DR. R. K. GLOCKER.

WISCONSIN DERMATOLOGICAL SOCIETY

Maurice Reuter, M.D., *President*

Donald M. Ruch, M.D., *Secretary*

Feb. 7, 1953

Acute Lupus Erythematosus. Presented by MILWAUKEE COUNTY GENERAL HOSPITAL.

White girl, aged 16, since 1951 has had mitral stenosis, splenomegaly, generalized lymphadenopathy, hemolytic anemia, lupus erythematosus cells in the bone marrow. Good response to cortisone, but, after discontinuance, recurrence of all symptoms. Responds again and is currently kept on 125 mg. Reversal of albumin-globulin ratio. Cortisone has, apparently, no influence on cells.

Chronic Discoid Lupus Erythematosus. Presented by MILWAUKEE COUNTY GENERAL HOSPITAL.

Tuberculous girl. Good response to quinacrine (Atabrine). Demonstration of fluorescence of nails in Wood's light.

Psoriasis, Arsenical Keratosis, and Malignant Tumors. Presented by VETERANS ADMINISTRATION, Wood, Wis.

White man, psoriasis for at least 30 years. Twenty years ago, took potassium arsenate (Fowler's) solution. One and a half years ago, basal cell carcinoma of left nipple treated by mastectomy. At present, extensive psoriasis, many keratoses of palms and soles. At right thumb, necrotic squamous cell carcinoma.

Trichoepithelioma Paplosum Multiplex. Presented by DR. DAVID BLIEL.

Disfiguring papular eruptions of the face. Father, brother, and sister also affected.

Atopic Dermatitis with Kaposi's Varicelliform Eruption. Presented by DR. O. H. FOERSTER, DR. H. R. FOERSTER, and DR. DONALD M. RUCH.

Girl, 17, probably contracted condition from cold sore of boy friend.

Bullous Eruption. Presented by DR. O. H. FOERSTER, DR. H. R. FOERSTER, and DR. DONALD M. RUCH.

Boy, aged 5 months. Eruption started, at one week of age, on ears; spread to heels, mouth, palms, fingers. From vesicles in mouth, hemolytic Streptococcus isolated. Penicillin brought little improvement. New bullae and vesicles formed continuously, especially on arms and legs. No history of consanguinity. At present, hemorrhagic and bullous lesions on hands, soles, margins of diaper area, and gluteal folds. (In the discussion several members suggested epidermolysis bullosa hereditaria.)

Kaposi's Varicelliform Eruption. Presented by DR. O. H. FOERSTER, DR. H. R. FOERSTER, and DR. DONALD M. RUCH.

Demonstration of Kodachrome. Boy, 17 months old, with "eczema" and superimposed herpetic infection. Favorable outcome under treatment with blood transfusions, Polysporin ointment (containing polymixin B and bacitracin), and Dicrysticin (a penicillin and dihydrostreptomycin preparation).

DISCUSSION

DR. DONALD M. RUCH: Penicillin is indicated because of the secondary infection. Streptomycin is indicated to combat the Hemophilus influenzae and the Escherichia coli, which also may cause death in this condition. Corticotropin and cortisone are contraindicated. They tend to disseminate the virus throughout the body and disturb the antibody reaction, thus destroying the natural immunity and immune bodies that the patient may develop. Chlortetracycline (Aureomycin) by mouth and locally is of little value.

Psoriasis. Presented by Dr. Sidney J. Kaplan, Kenosha.

Restricted to hands only, extremely resistant to therapy. Histological demonstration.

Keratosis Pilaris. Presented by Dr. Sidney J. Kaplan, Kenosha.

Child, 4 years, with scattered and grouped follicular keratoses on shoulders and extensor surfaces. Good response to cod liver oil, but recurrence. (In discussion several members suggested lichen scrofulosorum, especially with regard to history of tuberculosis in the families of both parents.)

Benign Pemphigus. Presented by Dr. Marvin S. Kagen, Appleton.

Man, 54, during last year had pemphigus with bullous involvement of the conjunctivae of mouth and neck. Course so far benign. The eyes responded well to cortisone drops.

Systemic Blastomycosis. Presented by Dr. Maurice Reuter and Dr. Leonard Markson.

DISCUSSION

Dr. Sture Johnson, Madison: In a patient of ours, to whom large amounts of iodides had been given orally and intravenously, iodism developed. We then gave diethylstilbestrol, 15 mg. daily for 10 weeks, without any change in the patient's cutaneous blastomycosis. After this failure, stilbamidine was given, with excellent results. The patient received three courses of stilbamidine. Each course consisted of giving intravenously 150 mg. of the drug daily for 10 days. On his last admission, three months after the third course, two new lesions had developed in which the organism of blastomycosis were present. From the results obtained to date, I would say that stilbamidine seems to be excellent in the treatment of blastomycosis, but that longer schedules are probably necessary to completely cure some patients.

Trichoepithelioma of Nose. Presented by Dr. Kurt Wiener.

Resembling rhinoscleroma, locally malignant large tumor. After two operations and electrosurgery, recurrence. Unexpectedly good result from deep x-ray therapy, 3,600 r, 0.5 mm. Cu Kodachrome and histological demonstration.

Benign Familial Pemphigus. Presented by Dr. Kurt Wiener.

Kodachrome and histological demonstration of biopsy tissue taken from bullous lesion of the neck of a man who has been suffering for 15 years from continual bullous outbreaks about the neck. His daughter is similarly affected.

Morphea. Presented by Dr. Leonard S. Markson.

Morphea, confirmed by biopsy. Bismuth sodium triglycollamate (Bistrimate), alpha-tocopherol, pilocarpine ointment; little success.

Lichen Ruber Moniliformis. Presented by Dr. Leonard S. Markson.

Woman, aged 52. Eruption started in 1945 at age 45 on elbows, shoulders, and nuchal area; slowly progressive; now covering most of the body. The pressure area around the waist is relatively free. The dense eruption consists of skin-colored, firm, discrete, semiglobular papules. No response to many types of therapy. No biopsy could be obtained.

Lichen Amyloidosus. Presented by Dr. Carlton S. Bolles, Green Bay.

Eruption for 15 years on both legs. Clinically suggestive of lichen planus acneformis; histologically, amyloid deposits. Extremely itchy. All treatment without effect.

Sarcoid or Tuberculosis? Presented by Dr. James J. Barrock.

Poikiloderma Atrophicans Vasculare? Lymphoblastoma? Presented by Dr. Marvin S. Kagen, Appleton.

Congenital Nodules of the Scalp. Presented by Dr. Harold Miller.

Lichen Nitidus. Presented by Dr. Maurice Reuter.

Bullous Eruption After "666." Presented by Dr. Joel Taxman.

Scleroderma with Ectopic Ossification. Presented by Dr. Kurt Wiener.

Cutaneous Blastomycosis. Presented by Dr. Leonard Markson.

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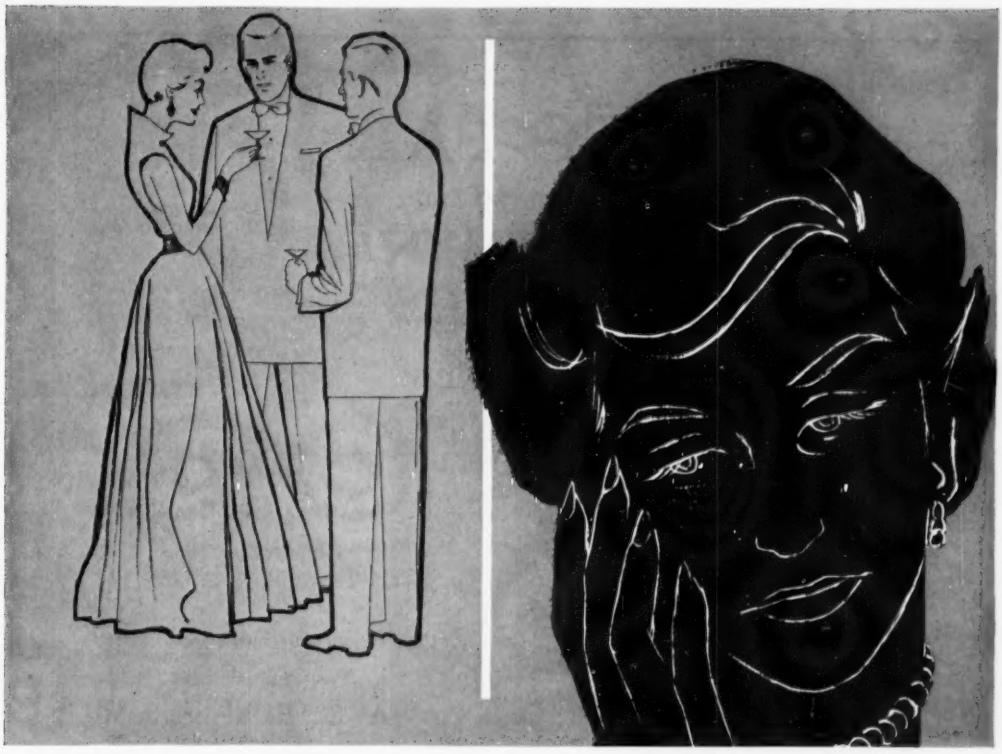

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1. Ellis, C. C., and others: The Treatment of Psoriasis with Liquor Carbonis Detergens, J. Invest. Dermat. *10*:455, 1948.

2. Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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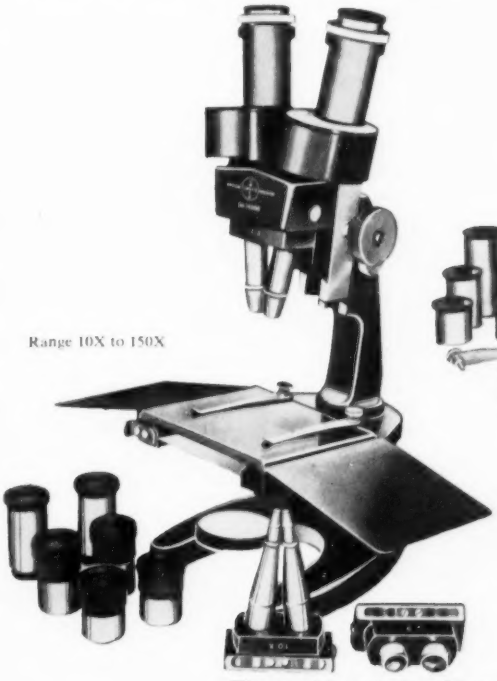

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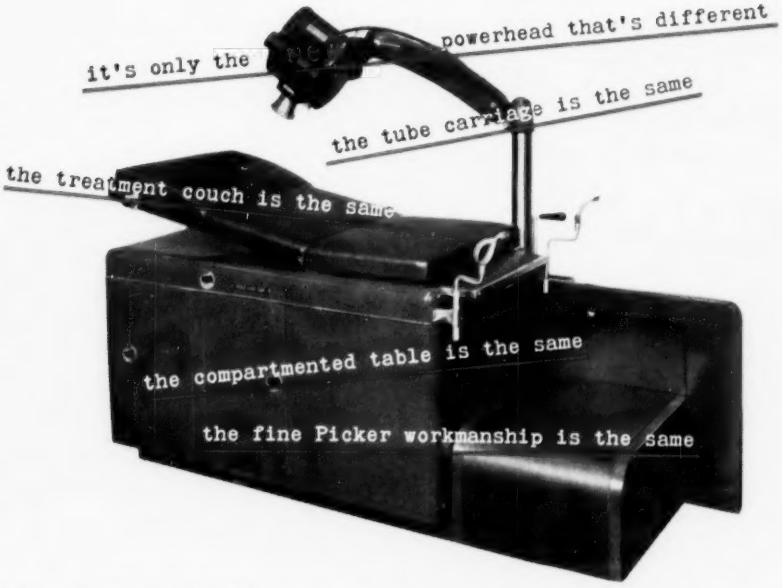
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